MIGRAINE COMORBIDITIES

A CLINICAL AND MOLECULAR GENETIC STUDY

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ACADEMIC DISSERTATION

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The thesis contains also some unpublished data

ABBREVATIONS

CAD	cervical artery dissection
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy
CSD	cortical spreading depression
CVD	cardiovascular disease
EQV	migraine equivalents
FHM	familial hemiplegic migraine
FMGP	Finnish migraine gene project
FMSQFS	Finnish migraine specific questionnaire for family studies
GABA	gamma aminobutyric acid
GAD	generalized anxiety disorder
GPT	gabapentin
GWA	genome wide association
HA	headache other than migraine
HM	hemiplegic migraine
ICHD-II	International Criteria for Headache Disorder, 2nd edition
IHS	international headache society
IS	ischemic stroke
LCA	latent class analysis
LTG	lamotrigine
MA	migraine with aura
MA+MO	migraine fulfilling the criteria of both migraine with and without aura
MELAS	mitochondrial encephalopathy, lactic acidosis and strokelike episodes
MI	migrainous infarction
MO	migraine without aura
MS	multiple sclerosis
MVP	mitral valve prolapse
NIHSS	National Institutes of Health Stroke Scale
NO	no headache
NSAID	nonsteroidal anti-inflammatory drugs
PET	positron emission tomography
PFO	patent foramen ovale
RLS	right-to-left shunt
SHM	sporadic hemiplegic migraine
TCA	trait component analysis
TEE	transesophageal echocardiography
TGVS	trigeminovascular system
TPM	topiramate
UNC	migraine with aura not fulfilling the current criteria (unclassified)
VPA	valproic acid

ABSTRACT

Migraine is a highly prevalent disease, and despite several important breakthroughs there are still a many questions unanswered in the clinical, genetic and pathophysiological aspects of migraine research. Migraine has been linked to several other diseases such as epilepsy and stroke, but there are still unsolved issues concerning the true nature of these associations. Three genes predisposing to hemiplegic migraine and several loci associated to migraine have been identified, but so far no genes responsible for common forms of migraine have been recognized. Triptans have provided an important step in migraine treatment, but their usefulness in rare forms of migraine have been controversial.

The Finnish Migraine Gene Project (FMGP) includes more than 1600 families and 7500 individuals. We evaluated comorbidity from 1000 consecutive subjects in the FMGP. To search for novel loci, we performed a genome-wide linkage scan in 36 families with high prevalences of migraine with visual aura. We collected 76 subjects from the FMGP who suffer from hemiplegic migraine and have used triptans. Finally, to study possible links between stroke and migraine we evaluated the prevalence of migraine in subjects with cervical artery dissection (CAD) and healthy controls.

Migraine was associated with increased prevalence of allergy, hypotension and psychiatric diseases. Additionally, men suffering from migraine with aura had increased prevalence of epilepsy and stroke. Further evidence of association between migraine and epilepsy was found in our linkage study. The parametric two-point linkage analysis showed significant evidence of linkage between migraine aura and a locus on 9q21-q22. Interestingly, the same locus has been associated with occipitotemporal epilepsy. CAD seems to be a migraine risk factor, and therefore a link between stroke and migraine. Notably, CAD seems to alleviate migraine activity further indicating the association between these two conditions. Despite the contraindications of triptans, it seems that they are safe and effective in the abortive treatment of hemiplegic migraine.

INTRODUCTION

Migraine is a painful and disabling disease. It is highly prevalent worldwide among people of working age and therefore causes a significant economical burden and a remarkable decrease in quality of life. In recent decades there has been great success in migraine research, but still there is an enormous need for better treatments and lack of understanding of the mechanisms and genetic background of the disease. Studying the comorbidity of migraine is one possible method to better elucidate such mechanisms. Previously migraine has been associated with several conditions, such as immunological and psychiatric disorders, and importantly to two other brain diseases, epilepsy and ischemic stroke.

For several decades the leading theory of migraine mechanism was Wolff's vascular theory. The idea was that vasoconstriction causes migraine aura and the following vasodilatation would cause throbbing headache. After breakthroughs in genetics, imaging and functional studies in migraine, the emphasis shifted for several years to neuronal mechanisms and the vascular theory was almost completely rejected. Recently direction has turned again to the vascular system, but the neuronal theory is as well accepted as before and thus migraine should perhaps be considered a neurovascular or vasculoneuronal disease. The idea of this study is to shed light on migraine mechanisms from both of these directions by evaluating the associations of migraine to both neuronal and vascular phenomena.

1 Classification and clinical features of migraine

1.1 Migraine with and without aura

Migraine is in its best fascinating, but in its worst severely disabling disorder. It is highly prevalent globally. Migraine attacks typically includes several phases: i) premonitory symptoms, ii) aura, iii) headache, and iv) postdromal symptoms. The common forms of migraine are migraine with aura (MA) and migraine without aura (MO). The most important differentiating feature between the two is a lack of the aura phase in subjects with MO, however, often the same individuals suffer from both kinds of attacks. The introduction of the International Criteria for Headache Disorders (ICHD) by the International Headache Society (IHS) diagnostic criteria in 1988 (1) (Table 1) was an important step for the reliability and reproducibility of clinical migraine studies and the criteria was updated 16 years later (ICHD-II, 2004) (2).

Table 1. International classification of migraine (ICD-10 code G43)

	ICD-10 CODE	DIAGNOSIS
1.1	G43.0	Migraine without aura
1.2	G43.1	Migraine with aura
1.2.1	G43.10	Typical aura with migraine headache
1.2.2	G43.10	Typical aura with non-migraine headache
1.2.3	G43.104	Typical aura without headache
1.2.4	G43.105	Familial hemiplegic migraine (FHM)
1.2.5	G43.105	Sporadic hemiplegic migraine
1.2.6	G43.103	Basilar-type migraine
1.3	G43.82	Childhood periodic syndromes that are commonly precursors of migraine
1.3.1	G43.82	Cyclical vomiting
1.3.2	G43.820	Abdominal migraine
1.3.3	G43.821	Benign paroxysmal vertigo of childhood
1.4	G43.81	Retinal migraine
1.5	G43.3	Complications of migraine
1.5.1	G43.3	Chronic migraine
1.5.2	G43.2	Status migrainosus
1.5.3	G43.3	Persistent aura without infarction
1.5.4	G43.3	Migrainous infarction
1.5.5	G43.3 + G40.x or G41.x	Migraine-triggered seizure
1.6	G43.83	Probable migraine
1.6.1	G43.83	Probable migraine without aura
1.6.2	G43.83	Probable migraine with aura
1.6.5	G43.83	Probable chronic migraine

According to the IHS criteria, migraine attacks last 4-72 hours and they typically include the following clinical features: a pulsating nature and an unilateral location of headache, moderate or severe intensity of pain, aggravation by physical activity, nausea and/or vomiting, and sensitiveness of senses (table 2.). Typical triggering factors for migraine attacks include stress, menstruation, certain foods, sensory stimuli, irregular eating, lack of sleep and oversleeping. Premonitory symptoms may precede actual aura and/or headache phase of the migraine attack by several hours and even days. Premonitory symptoms typically include a various combinations of fatigue, sensitiveness of senses, yawning, nausea, craving for foods and pallor (figure 1).

Table 2. Diagnostic criteria of migraine without aura according to International Criteria for Headache Disorders (ICHD-II) society diagnostic criteria of migraine without aura published by the International Headache Society.

A. At least 5 attacks1 fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D. During headache at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia
E. Not attributed to another disorder

Migraine aura consists of reversible and gradually developing neurological symptoms lasting at least several minutes and less than an hour. They include visual, sensory, and/or language disturbances (table 3.). The most common symptom is scintillating scotoma. Subjects with MA might experience several kinds of attacks: aura without headache, aura with typical migraine headache, aura with headache not fulfilling the IHS criteria of migraine headache as well as MO attacks. Typically subjects with MA consider the aura phase more disturbing than the headache phase of the migraine attack.

Table 3. Diagnostic criteria of migraine with aura according to International Criteria for Headache Disorders (ICHD-II) published by the International Headache Society.

A. At least 2 attacks fulfilling criteria B–D
B. Aura consisting of at least one of the following, but no motor weakness:
1. Fully reversible visual symptoms including positive features (eg, flickering lights, spots or lines) and/or negative features (ie, loss of vision)
2. Fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
3. Fully reversible dysphasic speech disturbance
C. At least two of the following:
1. Homonymous visual symptoms and/or unilateral sensory symptoms
2. At least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
3. Each symptom lasts ≥5 and ≤60 minutes
D. Headache fulfilling criteria B–D for 1.1 Migraine without aura begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder

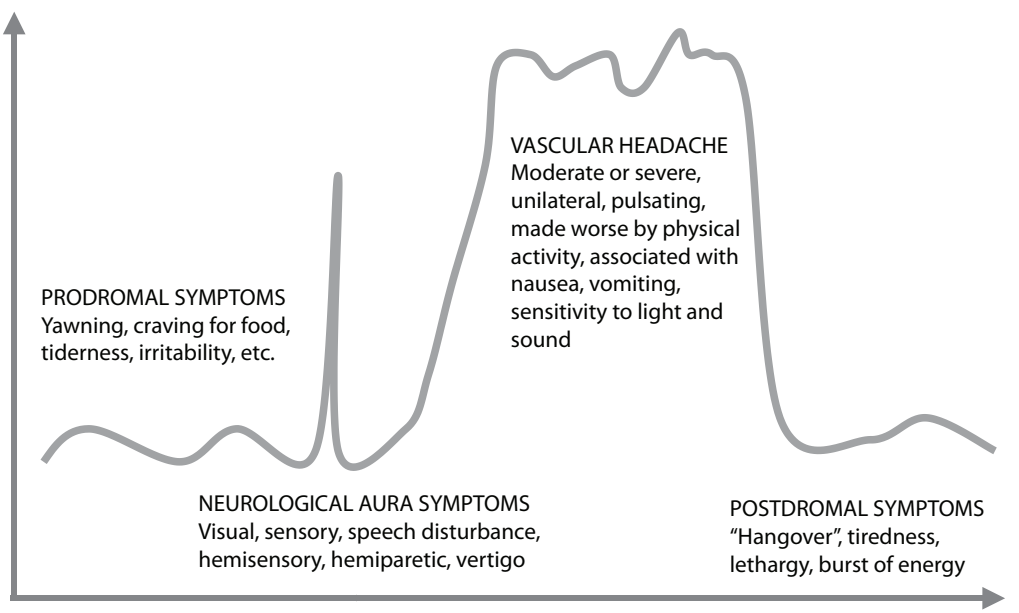


Figure 1. Features of migraine attack in different phases.

Table 4. Diagnostic criteria of familial hemiplegic migraine according to International Criteria for Headache Disorders (ICHD-II) published by the International Headache Society.

A. At least 2 attacks fulfilling criteria B and C
B. Aura consisting of fully reversible motor weakness and at least one of the following:
1. Fully reversible visual symptoms including positive features (eg, flickering lights, spots or lines) and/or negative features (ie, loss of vision)
2. Fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
3. Fully reversible dysphasic speech disturbance
C. At least two of the following:
1. At least one aura symptom develops gradually over 5 minutes and/or different aura symptoms occur in succession over 5 minutes
2. Each aura symptom lasts ≥5 minutes and ≤24 hours
3. Headache fulfilling criteria B–D for 1.1 Migraine without aura begins during the aura or follows onset of aura within 60 minutes
D. At least one first- or second-degree relative has had attacks fulfilling these criteria A–E
E. Not attributed to another disorder

1.2 Familial and sporadic hemiplegic migraine

Familial hemiplegic migraine (FHM) is a rare, autosomal dominantly inherited subtype of migraine with aura. In FHM at least some attacks are associated with one-sided motor weakness of varying severity (table 4.) (2, 3).

A separate rare migraine subtype is sporadic hemiplegic migraine (SHM), which is similar to FHM but there is no family history of analogous attacks (4). A large Danish epidemiological survey found that the prevalence of hemiplegic migraine (HM) in Denmark is 0.01%. The familial and sporadic forms were equally frequent (5). Other than motor symptoms 90 % of HM patients report visual, 80 % dysphasic and 70 % basilar symptoms as a part of their migraine aura (6). Additionally encephalopathy, coma, confusion, seizures, prolonged auras, cerebellar symptoms and mental retardation are also a part of the reported spectrum of HM phenotypes (7).

Mutations in three ion transporter genes, *CACNA1A*, *ATP1A2* and *SCNA1A* genes, cause FHM type 1, 2 and 3 respectively (8-10). The same genes, and especially *ATP1A2*, have also been indicated in SHM (11). Because of the wide spectrum of clinical manifestations and the lack of genetic similarities, it has been suggested that FHM should not be considered as a subtype of MA. It should rather be considered as a one of the syndromic migraines (12) even though family members of FHM patients seem to have an increased risk of MA, which suggests a shared genetic background (13).

2 Epidemiology of migraine

Migraine and other primary headaches such as tension type headache (TTH) are common diseases and headache is estimated to be the most prevalent neurological symptom (14). A lifetime prevalence globally has been reported to be 66% for headache and 46% for TTH (15).

There are no biological markers for migraine or other primary headaches. Therefore the IHS standardized diagnostic criteria by IHS from 1988 was crucial for comparable studies in headache epidemiology. Incidence rates reported for migraine were 580-601 per 100 000 person-years in women and 160-222 per 100 000 person-years in men in two studies performed in Denmark and the U.S. (16, 17). The incidence was highest in childhood and adolescence peaking earlier among boys (16). In a longitudinal population-based study in Denmark, the reported annual incidence for migraine was 8.1 per 1000 person years (18).

The first study of migraine prevalence using the IHCD was performed in Denmark and showed that the one-year prevalence is 6% in men and 15% in women (19). Stewart *et al.* investigated the one-year prevalence in the U.S. performing a large scale study by mailing questionnaires to 15 000 households (20). Of 20 468 participants, 17.6% of women and 5.7% of men fulfilled the ICHD-II for migraine. Prevalence was highest in individuals ages from 35 to 45. Furthermore, households having the lowest incomes had an elevated risk of migraine. Since then, numerous studies have been published from different countries with analogous results (21)

Most of the studies on migraine epidemiology do not separate the prevalence figures of MA and MO. A small study in Finland found that the one-year prevalence of MA is 8% in women and 2% in men, but the study was performed before the ICHD was published (22). Analogous results were reported in larger Danish study in which 7% of women and 4% of men studied had MA (23). Further studies have concluded that the prevalence of MA is less than one-third of the total migraine prevalence (21).

3 Pathophysiology of migraine

The classical idea of migraine pathophysiology was the vascular theory of migraine by H.G. Wolff in the 1940s. The original hypothesis was that vasoconstriction first causes migraine aura, which is then followed by compensatory vasodilatation inducing migraine headache. However, migraine attacks are more than just a combination of aura and headache. It is often preceded by premonitory symptoms such as fatigue, phonophobia and yawning, and is followed by postdromal symptoms, which supports the role of a central

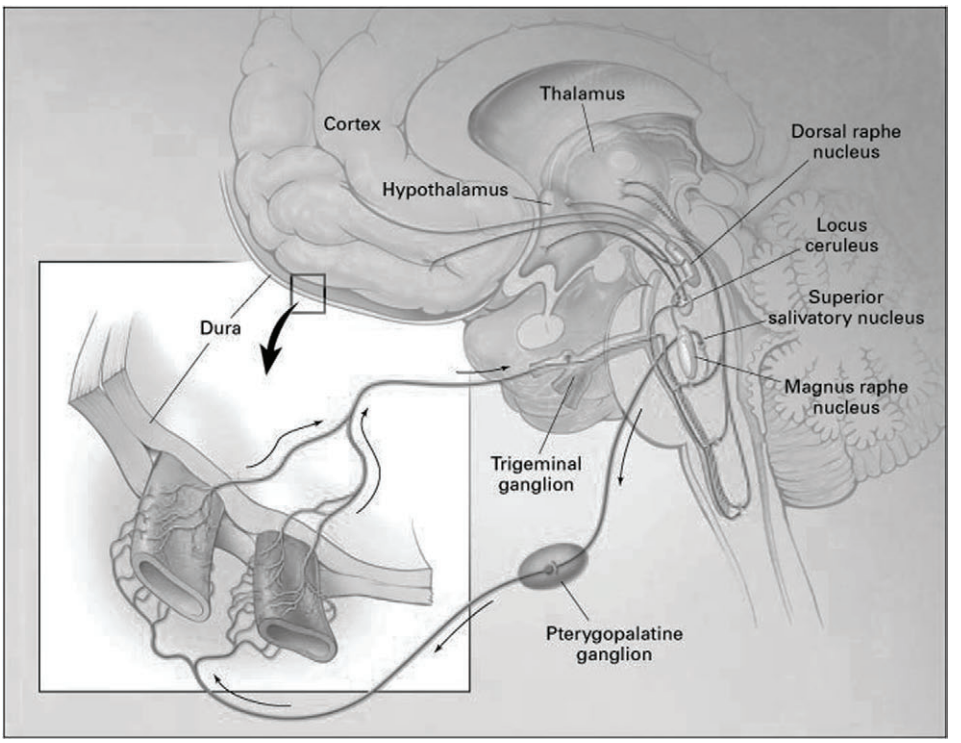


Figure 2. Illustration of the relevant anatomical structures involved in migraine pathophysiology. Copyright © [2002] Massachusetts Medical Society. All rights reserved. (Reprinted with a permission from New England Journal of Medicine) (29).

mechanism over merely disturbances in intracranial vessels. Furthermore, a report demonstrating that changes in blood flow and migraine symptoms are not associated suggests neuronal or neurovascular pathologies over just a vascular pathology behind the migraine attacks (24). The headache phase of migraine attacks have actually been reported to be better associated to hypoperfusion than to hyperperfusion in positron emission tomography (PET) studies (25).

The premonitory symptoms and episodic nature of migraine raised a suspicion of important roles of the hypothalamus and brainstem in the activation of migraine symptoms, which have since been confirmed by a PET imaging study (26). Therefore, headache is probably a consequence of activation of the trigeminovascular system (TGVS).

Migraine aura is believed to be a consequence of cortical spreading depression (CSD). CSD has been demonstrated with animal models as early as 1940s in the form of a slowly propagating (2 to 6 mm per minute) depolarization wave (27). A brief hyperemia is followed by oligemia and neuronal suppression. Even though the link between CSD and the headache phase of a migraine attack is poorly understood in humans, there are studies demonstrating CSD-inducing activation of TGVS in rats (28).

4 Genetics of migraine

Familial clustering and twin studies suggest that genetic mechanisms are involved in migraine and especially in MA (30). Many studies conducted earlier have, however, not applied the IHS criteria and make no distinction between MA and MO. A Danish population-based study addressed the heredity of migraine using the ICHD-II criteria and found that familial risk is different in MA and MO. Relatives of probands with MO had 1,9 times risk for MO, and relatives of probands with MA had an almost four times greater risk of MA but no increasing risk of MO, suggesting that MA and MO have different etiologies (31). MO seems to be a consequence of both genetic and environmental factors, whereas MA seems to depend more on genetic factors. However, they should still both be considered multifactorial diseases. Interestingly, also spouses of MO patients have a slightly elevated risk of MO.

Several population-based twin studies (32-36) have examined the concordance of migraine in monozygotic twins. Mulder *et al.* studied the prevalence and heritability of migraine in 29717 twin pairs from six countries that participated in the GenomEUtwin project (32). The prevalence of migraine was highest, 32-34%, in Danish and Dutch women and lowest, 10-13%, in Finland. The heritability was 34-57%. Two studies on Danish twins diagnosed using the ICHD-II criteria reported higher pairwise concordance rates in monozygotic than in dizygotic twin pairs, thereby providing additional support for the idea that genetic factors are involved in both MA and MO (33, 35).

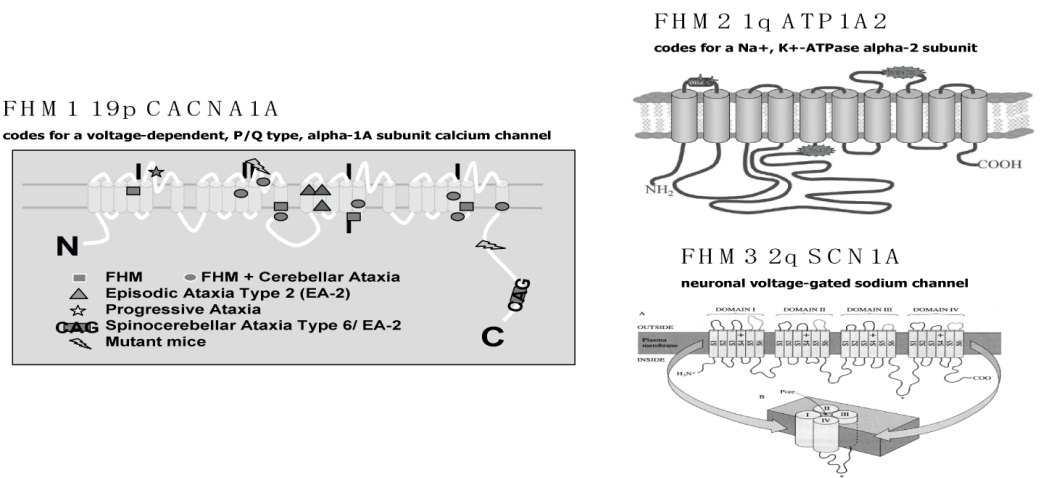


Figure 3. Two ion-channel genes CACNA1A and SCN1A and one coding for an ATP exchanger, ATP1A2 have been found to underlie Familial Hemiplegic Migraine.

Samples of cases and controls and families have been used to identify susceptibility loci and genes involved in migraine etiology. Despite numerous candidate gene association studies, the only variant associated with MA in several populations to date is a polymorphism in the *MTHFR* gene on chromosome 1p36 (37). A Finnish and a German study, however, have not confirmed the association between migraine and the *MTHFR* C677T variant (38, 39). Three ion-transporter genes, on the other hand, have been associated with FHM, a rare mendelian subtype of MA characterized by hemiparesis as a part of aura (figure 3). Ophoff *et al.* were the first to discover that missense mutations in the *CACNA1A* gene, encoding the α subunit of a voltage-gated Ca2+ channel (FHM type 1) (8), can cause FHM. Mutations in *CACNA1A* are also associated with episodic ataxia type 2 and spinocerebellar ataxia type 6. FHM type 2 is caused by mutations in *ATP1A2*, which encodes the α2 subunit of Na+/K+ ATPase (9). The third FHM gene, *SCN1A*, encodes the pore-forming α1 subunit of the neuronal voltage-gated sodium channel (10). These findings have lead to the idea that common types of migraine might be channelopathies. Even though some individuals with *CACNA1A* mutations

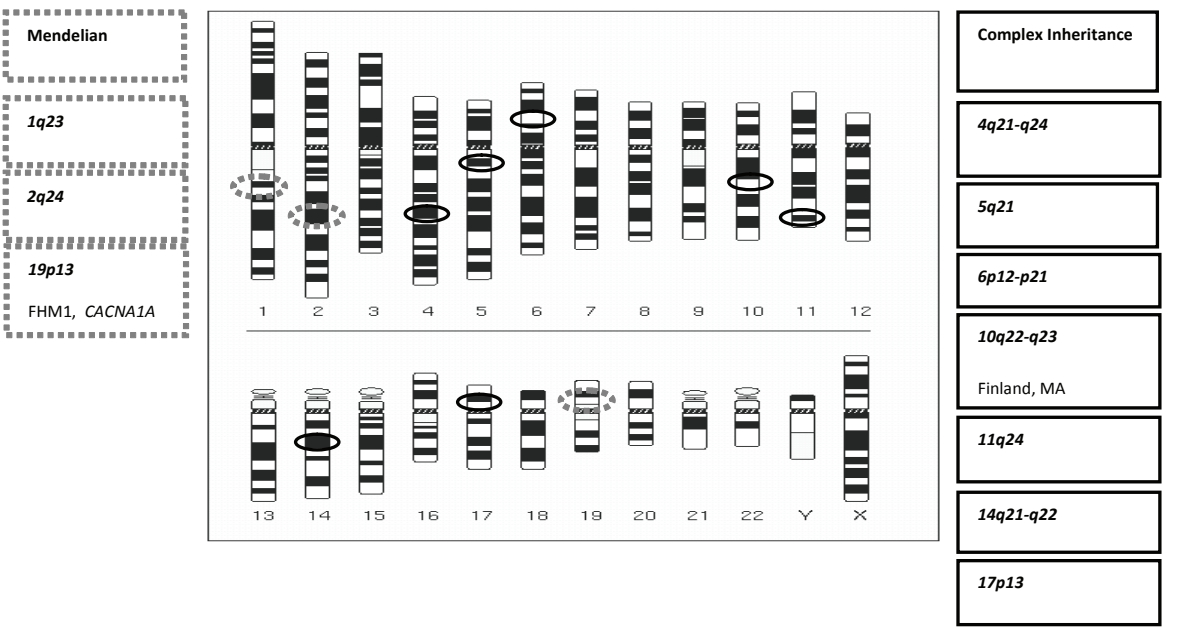


Figure 4. Susceptibility loci and genes identified for migraine. The dashed circles show the chromosomal locations of the three known FHM genes in the human genome. The solid black circles indicate the chromosomal loci that have shown significant evidence of linkage either to MA or MO in genome-wide scans.

in FHM families have a phenotype comparable of MA or MO, most of the linkage studies have not indicated evidence of the involvement of the FHM genes in common types of migraine (30). Furthermore, a previous Finnish study indicates that common variants in ion channel genes do not have a major role in MA susceptibility (40).

Besides FHM, these genes have also been associated with epileptic seizures. Mutations in *CACNA1A* are known to cause epileptic seizures (8, 41), *ATP1A2* (9) is associated to benign familial infantile convulsions (42) and *SCN1A* (10) is associated with generalized epilepsy with febrile seizures plus and severe myoclonic epilepsy of infancy.

Genes predisposing to MA or MO have not yet been identified although several loci have been indicated in the genome-wide linkage analyses (figure 4). Evidence of significant linkage has been found between a locus on chromosome 4q24 in Finnish MA families (43). A region close to this locus, 4q21, has been linked to MO in Icelandic families (44). In addition to locus/loci on 4q, several other chromosomal loci, shown in Fig 4, have shown significant evidence of linkage either to MA or MO (45-47).

The International Migraine Genetics Consortium has launched a genome-wide association study (GWA) spanning three European populations (Finnish, Dutch, and German) to study the role of common single nucleotide polymorphisms in migraine. The Finnish sample consists of over 1000 MA cases and over 4000 non-migraneous controls.

The identification of genes associated with migraine is obviously challenging, as with other complex diseases. The lack of replication of identified migraine loci may be due to phenotypic and genetic heterogeneity of migraine. Even the use of ICHD-II phenotypes, as in most of the molecular genetic studies of migraine, has not helped identify susceptibility genes in common forms of migraine. Alternative approaches have thus been suggested to deconstruct the end diagnosis of migraine. In latent-class analysis (LCA), individuals are classified into empirically derived groups on the basis of patterns of ICHD-II symptom clustering observed in a large Australian twin sample. Using this approach, Nyholt *et al.* have found significant evidence of linkage to chromosome 5q21. They have also provided evidence for other new loci and confirmed previously reported loci influencing common migraine (48, 49).

Another approach, trait component analysis (TCA), applies clinical information of individual traits in the ICHD-II symptom data in order to classify patients into groups. Using this method and reanalyzing 50 Finnish MA families, Anttila *et al.* detected significant evidence of linkage between a locus on chromosome 17p13 and trait pulsation. The previous study on these families had indicated nominal evidence of linkage between MA end diag-

nosis and 17p13 (50). A recent study by Anttila *et al.* with three different strategies (clinical end-diagnosis, TCA and LCA) detected significant evidence of linkage to chromosome 10q22-q23 and the finding was replicated in two separate population samples from Finland and Australia (51).

The LCA and TCA methods have so far been used only in linkage studies of migraine families where they have successfully identified new loci and replicated known migraine susceptibility loci. Case-control studies of genetic variants are, on the other hand, more suitable for effect-size estimation. In the near future GWA on common migraine may clarify the role of single gene variants to specific traits.

5 Treatment of migraine

Treatment of migraine includes pharmacological and non-pharmacological treatments. The latter involves avoiding triggering factors and other life-style modifications as well as treatments such as acupuncture. Pharmacological treatments include acute and preventive agents. Different acute medications and their recommended doses following current treatment guidelines are listed in table 5.

5.1 Selective 5-HT1B/1D agonists (triptans)

Abortive pharmacological treatment of migraine can be divided into two main classes (52). The Ergot alkaloids (used since 1926) and triptans (used since 1991) are considered to be migraine-specific treatments while the nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol are non-specific.

The first triptan introduced was sumatriptan (53) and six more have since become available: zolmitriptan (54), rizatriptan (55), eletriptan (56), naratriptan (57), almotriptan (58) and frovatriptan (59) (table 5). Triptans are 5-HT1B/1D agonists and in Finland they are considered to be first-line treatment for severe migraine attacks due to their efficacy and tolerability. They have multiple mechanisms of action, including vasoconstriction of dilated cerebral blood vessels, inhibition of the release of vasoactive neuropeptides by trigeminal nerves and inhibition of nociceptive neurotransmission (60). They all have the same contraindications: ischemic heart disease, ischemic stroke, Prinzmetal`s angina, uncontrolled hypertension, pregnancy, basilar migraine and hemiplegic migraine. They are considered safe and well tolerated when used correctly (61) and do not increase the risk of stroke, myocardial infarction, cardiovascular death, ischemic heart disease and mortality (62).

5.2 Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are probably the most commonly used acute medications for migraine. NSAIDs block cyclo-oxygenase and thereby inhibit the synthesis of prostaglandins from arachidonic acid. Convincing evidence of efficacy has been reported in agents such as acetylsalicylic acid (63), diclofenac (64), ibuprofen (65), and naproxen (66) (table 5).

5.3 Paracetamol

Paracetamol is a widely used over-the-counter analgesic and antipyretic. It has been reported to be more effective than a placebo when combined with metoclopramide (67) or codeine (68), but not alone (69). It has been shown to have a similar efficacy as acetylsalicylic acid (70), but is less effective when compared to NSAID's (71).

5.4 Corticosteroids

The role of corticosteroids in the treatment of migraine and other headaches has been controversial. Small trials have demonstrated promising results for IV dexamethasone in headache recurrence prevention (72, 73), but recently Friedman *et al.* demonstrated in a 205-patient randomized placebo-controlled trial that 10 mg IV dexamethasone is not effective in acute migraine treatment (74). A recent meta-analysis suggests a modest, but significant, benefit when dexamethasone is added to standard antimigraine therapy (75). Another meta-analysis concluded that dexamethasone is not effective in pain alleviation, but it significantly reduces headache recurrence (76). Prednisolone has been found ineffective on withdrawal headache in patients with medication overuse and chronic daily headache (77). Supplementing dexamethasone treatment with rizatriptan has been reported to be more effective in treating menstrual migraine than rizatriptan alone (78). The theoretical background for the use of corticosteroids in migraine is based on observations that suggest a relationship between neurogenic inflammation and migraine (79, 80). Migraine has also been demonstrated to have comorbidity with inflammatory diseases such as allergy (81).

5.5 Antiemetic drugs

Nausea (with or without vomiting) is, besides pain, often one of the main symptoms in migraine attacks, and therefore, the idea of using antiemetics in migraine treatment seems reasonable. Another indication that they might be useful is the possible delayed absorption of per oral medication in migraine treatment due to gastric stasis (82). Antiemetics have been thought to support gastric emptying, thereby enhancing the efficacy of other per oral antimigraine medications such as triptans and NSAIDs (83).

Table 5. Acute medications of migraine. Modified from the Finnish current treatment guideline (90).

Severe or disabeling headache	Dosage (mg)
TRIPTANS	
almotriptan	12.5 p.o.
eletriptan	40–80 p.o.
frovatriptan	2.5 p.o.
naratriptan	2.5–5 p.o.
rizatriptan	5–10 p.o.
sumatriptan	50–100 p.o., 20 i.n., 25 p.r., 6 s.c.
zolmitriptan	2.5–5 p.o., 5 i.n.
ERGOTAMINES	
ergotamine	ad 2 p.o./p.r., ad 6/daily
dihydroergotamine	1 i.m. tai 0.5 i.v.
Mild or moderate headache	
ANTI-INFLAMMATORY MEDICATIONS	
acetylicsalicylic acid	1 000 p.o.
paracetamol	1 000 p.o./p.r.
diclofenac	50–75
ibuprofen	800–1 200
ketoprofen	100–200
naproxen	500–1 100
tolfenamic acid	200
ANTIEMETICS (in combination with agents above)	
metoclopramide	10–20 p.o./p.r.
prochlorperazine	10–25 p.o./p.r.

p.o.=per oral
i.n.=intranasal
s.c.=subcutaneously
p.r.=per rectally

Metoclopramide is a benzamide derivative which is a dopamine and 5-HT3 antagonist. Intravenous metoclopramide has been reported to be effective in a placebo-controlled study of migraine treatment (84) and in high doses it is comparable to subcutaneous sumatriptan treatment in an emergency department setting (85). Orally administered metoclopramide alone has not been proven to be superior to placebo (86) but it is beneficial as an adjunct therapy with both sumatriptan (87) and tolfenamic acid (86).

Another antiemetic drug prochlorperazine has been reported to be effective when administered intramuscularly or rectally. It is superior or comparable to metoclopramide when administered intramuscularly (88) or intravenously (89).

5.6 Treatment of hemiplegic migraine

Patients with basilar migraine or HM have been excluded from randomized controlled triptan trials. The rationale for this exclusion is the possibility that the triptans would aggravate cerebral vasoconstriction and enhance the risk of ischemic stroke. Therefore, there are no randomized controlled prospective studies evaluating the clinical use of triptans in HM. However Klapper *et al.* presented a case report of 13 patients with basilar migraine, FHM or migraine with prominent or prolonged aura who had received triptans with excellent results and without adverse events (91). There are anecdotal reports of treatment of HM with agents such as verpamil (92, 93) and azetazolamide (94) but neither prospective nor large studies have been performed. According to one theory, vasodilatating agents such as calcium channel blockers might work in the acute or preventive treatment of FHM, but a recent case report described a prolonged FHM attack after intravenous nimodipine infusion, suggesting caution (95).

5.7 Preventive treatment of migraine

The rationale of preventive medications in the treatment of migraine is to diminish the activity of migraine by several months lasting daily medication. Traditionally, preventive medication should be considered if patient has several (three or more) monthly attacks. The most commonly used treatments include antiepileptic medications, antidepressants and antihypertensive medications. Different prophylactic agents and dosages recommended in current treatment guideline are listed in table 6.

Antiepileptic drugs have been used in the treatment of migraine since the 1950s based on empirical evidence, but the efficacy and tolerability of agents, such as phenytoin and phenobarbital, were unsatisfactory. An early placebo-controlled study of carbamazepine in migraine prophylaxis was promising, reporting that 84 % (38/45) of the active treatment group improved compared to 27 % (13/48) in the control group (96). The strongest evidence of efficacy has been reported for valproic acid (VPA) and topiramate (TPM), but lamotrigine (LTG) has also been used, especially in the prophylaxis of auras (97). A Cochrane review concluded that antiepileptic drugs considered as a class reduce migraine frequency by 1,3 attacks per 28 days compared to placebo (98).

Valproic acid

Valproic acid (VPA) is an antiepileptic drug with a multiple mechanisms of action (99). Besides epilepsy and migraine it is commonly used in the treatment of bipolar disorder (100) and sometimes in the treatment of cluster headache (101). The precise mechanism in migraine alleviation is unclear, but the enhancement of GABAergic neuro-trans-

mission seems to be the most likely (102). VPA increases GABA levels in the central nervous system in several ways: by stimulating the GABA synthetic enzyme (glutamic acid decarboxylase) and by inhibiting the GABA degradative enzymes (GABA aminotransferase and succinate semialdehyde dehydrogenase) (102).

The first randomized and placebo-controlled study of VPA in the treatment of migraine was a small cross-over study in 29 migraine patients (table 2). The patients were given either 400 mg of VPA or a placebo for eight weeks and then crossed over for an additional eight weeks. Patients suffered 4,4 migraine attacks per month in the active treatment period compared to 7,8 attacks per month in the placebo period (103). The efficacy of VPA has been reported in different daily dosages (500-1500mg) (104-106). So far, the largest study on this subject was performed by Freitag *et al.* in a study of 237 migraine patients who were randomized to receive 500-1000 mg of extended release VPA daily (122 patients) or a placebo (115 patients) for 12 weeks. The main outcome was the reduction of migraine activity with the VPA group showing a greater reduction than the placebo group ($p < 0.006$). Importantly there were no significant differences in the incidence of adverse events between the groups (107). Small studies on acute treatment of migraine with intravenous VPA have been carried out, but the number of patients has been too limited to show convincing evidence of efficacy (108).

Topimarate

Topiramate (TPM) is a wide-spectrum antiepileptic drug with a multiple mechanisms of action. Potential migraine alleviation has been suspected resulting from its effects on voltage-gated sodium channels and the enhancement of the inhibitory GABA system.

Storey *et al.* reported the potential efficacy of TPM in migraine prophylaxis in a small randomized controlled study (109). The result has been confirmed in larger studies with several different daily doses tested (50mg, 100mg and 200mg) (110, 111) and efficacy has been reported to continue for up to 14 months (112). Diener *et al.* reported that while the number of monthly migraine days increases after cessation of the TPM treatment, they do not return to pre-treatment levels, suggesting sustained benefit even after discontinuing the treatment (113). Furthermore, TPM has been reported to be effective in the treatment of chronic migraine. In an Italian study, the average number of days with headache per month was reduced from 20,9 to 8,1 in subjects with a daily dosage of 50mg TPM (114) and results were confirmed by Silberstein *et al.* with a daily dose of 100mg TPM (115). The efficacy of TPM has been reported to be comparable to both propranolol in migraine prophylaxis (116) and VPA in the treatment of chronic migraine (117).

Gabapentin

Gabapentin (GPT) is an antiepileptic drug that modulates Ca2+ chan-

nels and increases GABAergic activation in the brain. Besides epilepsy GPT is commonly used in the treatment of neuropathic pain. After promising results in a small study of GPT in prophylactic treatment of migraine (118), Mathew *et al.* performed a randomized double-blind study in 143 migraine patients (119). The frequency of migraine decreased from 4,2 monthly attacks to 2,7 in patients receiving 2400 mg GPT daily and the difference was significant compared to patients receiving placebo in whom frequency decreased from 4,1 monthly attacks to 3,5.

Lamotrigine

Lamotrigine (LTG) is an antiepileptic drug that blocks voltage-sensitive sodium channels, which in turn inhibits the neuronal release of glutamate. Besides in partial and generalized epilepsy treatment, it has been used in treating bipolar disorder and neuropathic pain (100). Steiner *et al.* conducted a randomized trial with 77 patients having active migraine who received either 200 mg of LTG daily or a placebo for three months. Monthly attack frequency decreased by 0,4 (3,6-3,2) in LTG treatment group and by 1,4 (4,4-3,0) in the placebo group. Therefore, the study failed to prove the efficacy of LTG in the prophylactic treatment of migraine (120).

Glutamate is a neuroexcitatory amino acid and has been considered to play an essential role in the development of CSD, a biological phenomenon most likely causing migraine aura. Therefore, in the wake of the Steiner *et al.* study, it was believed LTG might only be useful in treating MA or aura alone. A small open study of 15 MA patients was set up to evaluate the efficacy of LTG in the prophylaxis of migraine aura. The reduction of aura symptoms was significant, from 1,3 per month to 0,1 per month over the four-month treatment period, as well as the shortening of aura from 23 minutes to 4 minutes (121). Similar results were reported also in a small Italian open study of 24 MA patients (122). Pascual *et al.* treated 47 MA patients with disturbing aura symptoms. A 50 % reduction of aura symptoms was considered positive response and it was observed in 68% of patients (123). A similar end point was used in an open study of 59 MA patients of which 75 % experienced a positive response (124). The frequency of migraine attacks was reduced from 2,1 to 1,2 per month and the median LTG daily dosage was 167 mg. Furthermore, there is a report suggesting the efficacy of LTG in epilepsy related auras (125).

Beta-blockers

Beta-blockers were primarily introduced to treat angina pectoris, arrhythmias and hypertension but the first reports of antimigraine effects are from as early as the sixties (126). Several different agents, such as propranolol, atenolol, metoprolol, bisoprolol and timolol, have been reported to be effective in migraine prophylaxis. A meta-analysis by Holroyd *et al.* concluded that propranolol reduced migraine activity by 44% compared to a 14% reduction in the placebo group

(127). Beta-blockers are considered especially good alternatives in migraineurs with hypertension or angina pectoris, whereas for subjects with asthma or psychiatric problems beta-blockers should be used only with caution.

Treatments affecting renine-angiotensin system

Both angiotensin-converting enzyme inhibitors (lisinopril) and angiotensin II receptor blockers (candesartan) have been shown to be effective in migraine prophylaxis (128, 129). Good tolerability makes candesartan especially useful in clinical practice.

Tricyclic antidepressants

Amitriptyline is a tricyclic antidepressant that inhibits both noradrenaline and 5-HT uptake. It has been reported to be effective in several randomized placebo-controlled trials (130). Sedation is a common side-effect and limits the usefulness of the agent in migraine prophylaxis, especially in higher dosages.

Table 6. Preventive treatments of migraine. Modified from the Finnish current treatment guideline (90).

TREATMENT	DOSAGE (mg/d)	EFFICACY
BETA BLOCKERS		
Propranolol	40-240	++
Metoprolol	47.5-190	++
Atenolol	50-150	++
Bisoprolol	5-10	++
TREATMENTS AFFECTING THE RENINE-ANGIOTENSIN SYSTEM		
Candesartan	8-32	+
Eprosartan	300-600	+
Lisinopril	5-20	+
CALCIUM-CHANNEL BLOCKERS		
Verapamil	160-230	+
Nifedipin	30-60	+/-
Nimodipin	30-120	+/-
Flunarizine	5-10	++
TRICYCLIC ANTIDEPRESSANTS		
Amitriptyline	10-50	++
Nortriptyline	10-50	+
ANTICONVULSANTS		
Valproate	500-1500	++
Topiramate	50-200	++

++=good evidence of efficacy
+=moderate evidence of efficacy
+/-=poor evidence of efficacy

6 Comorbidity of migraine

Medical disorders can share comorbidity several different ways; i) coincidently, ii) one may predispose another, iii) two conditions may share common pathophysiological, molecular genetic or environmental background.

6.1 Ischemic stroke

6.1.1 Epidemiology

Migraine is a typically benign disorder of young people and the prevalence is two to three times higher in women than in men. Ischemic stroke (IS) is more prevalent in men and it typically affects older people more than migraine. IS is also typically a more serious threat to the health of an individual compared to migraine. Nevertheless, the association between the two disorders has been known for a long time and is profoundly-studied with several cohort, case-control and longitudinal studies and two meta-analysis published (131-147). A meta-analysis by Etminan *et al.* concluded that subjects with both MA (RR 2.27, CI 95% 1.61-3.19) and MO (RR 1.83, CI 95% 1.06-3.15) have an increased risk of IS (146).

One of the first publications on this subject was a case-control study of 89 IS patients and 178 controls. The prevalence of migraine with aura (MA) was 13 % in IS patients and only 5 % in controls (RR 2,6, CI 95 % 1,1-6,6). There was no difference in the prevalence of migraine without aura (MO) between groups (table 7.) (131). A French case-control study of a 212 IS patients and 212 controls found significant association between IS and the prevalence of migraine in women under 45 years of age (132). Therefore, subsequent case-control studies have focused on young women (133-140).

A study of 308 young (15-44 years) IS patients and their age and gender matched controls reported a significantly elevated prevalence of MA in IS patients compared to the controls (OR 14,8), but there was no difference in the prevalence of MO (133). Another study using 72 young women with IS and 173 controls reported both MA (OR 6,2) and MO (3,0) as risk factors for IS. Furthermore, the risk of IS was substantially greater in women with migraine using oral contraceptives (OR 13,9) or those who were heavy smokers (OR 10,2) (134). However, a recent large-scale cohort study found no association between oral contraceptives and risk of IS (148). Carolei *et al.* studied the prevalence of migraine in 308 women under 45 with IS and in 591 controls. Migraine was more prevalent in IS patients than in controls (OR 1,9, 95 % CI 1,1-3,1), but the odds ratio was even higher in the subgroup of women under 35 (OR 3,7, 95 % CI 1,5-9,0) (136), suggesting an increasing importance of migraine as a stroke risk factor in younger age groups. The result of a Finnish study of 506 working age IS patients differed from other studies showing that migraine was stroke risk factor for stroke in men only (137).

Table 7. Migraine as a risk factor for ischemic stroke

STUDY	NO. OF STROKE PATIENTS (YEARS)	NO. OF CONTROLS	RR (95% CI)	COMMENT
Henrich et al. 1989	89 (18-65 years)	178	1.8 (0.9-3.6)	Only MA significant 2.6 (1.1-6.6)
Tzourio et al. 1993	212	212	1.3 (0.8-2.3)	significant only in young women 4.3 (1.2-16.3)
Marini et al. 1993	308 (15-44 years)	308	1.9 (1.0-3.5)	
Tzourio et al. 1995	72 (women under 45)	173	3.5 (1.8-6.4)	
Lidegaard et al. 1995	497 (women under 45)	1370	2.8 (2.0-4.2)	
Carolei et al. 1996	308 (women under 45)	591	1.9 (1.1-3.1)	
Haapaniemi et al. 1997	506 (16-60 years)	345	2.1 (1-2.9)	significant only in men
Chang et al. 1999	291 (women under 45)	736	3.5 (1.3-9.6)	
Donaghy et al. 2002	86 (women under 45)	214	2.9 (1.2-7.1)	
Schwaag et al. 2003	160 (under 46)	160	2.1 (1.1-3.8)	

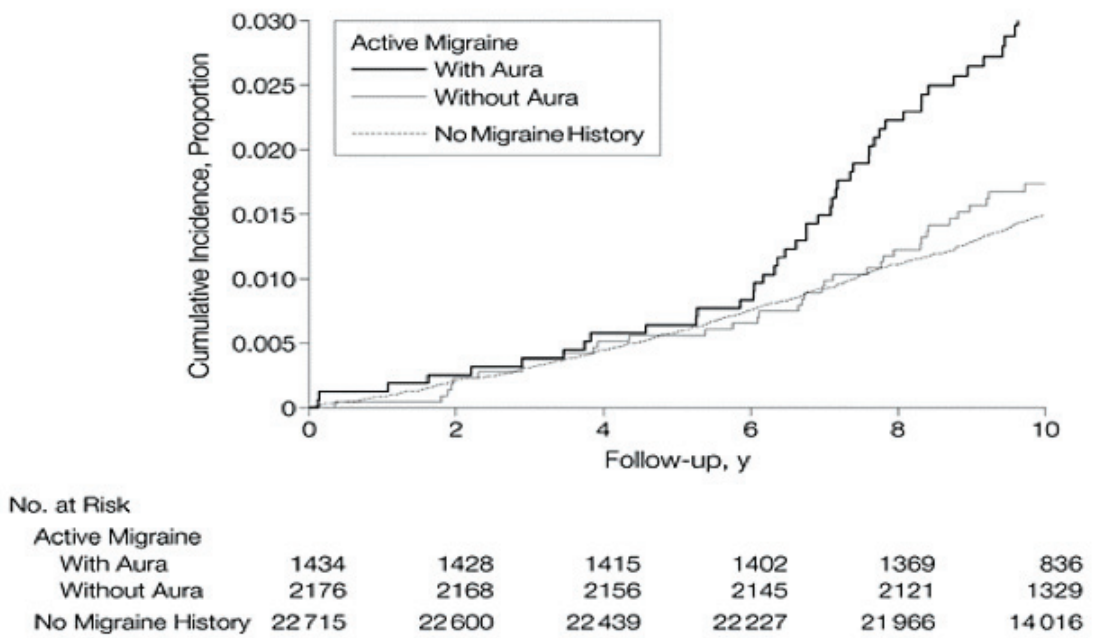


Figure 5. Cumulative incidence of cardiovascular events in women experiencing active migraine with or without aura and women without migraine (Jama, 296 (3) 283-91, 2006. Copyright © (2006) American Medical Association. All rights reserved) (149).

Cohort studies report similar results, suggesting that migraine approximately doubles the risk of IS compared to subjects without migraine (143-145). Figure 5 shows the incidence of cardiovascular events in women with MA, MO and without migraine in a large cohort study (149).

Two large longitudinal studies found significant association to IS only among subjects with MA (141, 142). Five years after Etminan's meta-analysis, a new meta-analysis by Schürks *et al.* (147) concluded that only MA was a significant risk factor for IS, not MO (table 8) (147). Young age, oral contraceptives and smoking further increased the relative risk. Migraine was only a risk factor among women.

6.1.2 Imaging

A Dutch CAMERA study in 2004 made news headlines in the U.S. The study included 161 MA patients, 134 MO patients and 140 healthy controls, non of which had a history of ischemic stroke symptoms (150). All patients were examined by brain MRI and blinded neuroradiologists estimated the amount of silent ischemic lesions and white matter lesions. Patients with migraine seemed to have slightly more silent ischemic lesions (8.1%) than controls (5.0%), but the difference was not significant. However, in the posterior circulation area migraineurs had seven times higher risk for silent ischemic lesions than controls. The difference was even greater in patients with active migraine (at least one migraine attack per month) and subjects with MA had an OR 15.8 for silent ischemic lesions in the posterior circulation (CI 95 % 1.8-140) (150). A meta-analysis of seven case-control studies reported that patients with migraine have a four-fold risk for white matter lesions than controls (151).

Table 8. Migraine and risk of cardiovascular events. Modified from a meta-analysis by Schürks et al. (147).

MIGRAINE TYPE AND VASCULAR EVENT	RELATIVE RISK (95% CI)
migraine and ischemic stroke	1.73 (1.31-2.29)
women	2.08 (1.13-3.84)
men	1.37 (0.89-2.11)
<45 years	2.65 (1.41-4.97)
current oral contraceptive use	7.02 (1.51-32.68)
smoking	9.03 (4.22-19.34)
migraine with aura	2.16 (1.53-3.03)
migraine without aura	1.23 (0.90-1.69)
migraine and hemorrhagic stroke	1.18 (0.87-1.60)

6.1.3 Patent foramen ovale

The comorbidity of MA, stroke and patent foramen ovale (PFO) as well as the implications of the comorbidity for clinical management has been a topic of considerable controversy in recent years. The epidemiological association of these conditions is well-documented (146, 152-155). Transcranial doppler and transesophageal echocardiography (TEE) studies have demonstrated significantly increased prevalence of right-to-left shunt (RLS) in patients with MA compared to the migraine-free control population (152, 153). Young patients with cryptogenic stroke have been reported to have a higher prevalence of PFO than healthy controls (155, 156), while MA has been associated with increased risk of ischemic stroke in several epidemiological studies (146).

It has been hypothesized that PFO might predispose to both MA and ischemic stroke through paradoxical microscopic emboli. Passage of chemical substances normally eliminated in the lungs has also been suggested to be a possible trigger of migraine. It has been reported that paradoxical emboli frequently end up in the posterior circulation (157), and furthermore, that MA patients with massive RLS tend to report that Valsalva-provoking activities trigger their MA attacks (158). Therefore, it is possible that visual auras are triggered by emboli that have traveled across the PFO, found their way to occipital areas via posterior circulation and caused cortical spreading depression (159).

Retrospective and open studies have reported promising results in decreasing migraine activity after closure of PFO (160). Therefore several prospective studies have been started. Results of the MIST-trial, the only randomized controlled study published thus far, was negative. The study included 147 patients with active migraine who were randomized into two groups: one undergoing the closure of PFO and the other receiving a sham procedure. The primary outcome of interest was whether patients experienced complete migraine remission, but there was no difference between the groups (3/74 in active treatment group and 3/73 in sham group) (161). Furthermore there were no difference among secondary outcomes either. However, recently Vigna *et al.* reported a study of 82 patients with migraine, subclinical brain lesions and PFO. The study was not randomized, but the decision over whether the PFO was closed was based on the patients' preferences. Migraine disappeared in 34% of the operated patients and 7% of controls (162). Importantly a recent large scale and the first population based study found no difference in prevalence of PFO between migraineours and controls (163).

6.1.4 Cervical artery dissection (CAD)

In general atherosclerosis and cardiac embolism are the most common etiologies of ischemic stroke, but in young adults cervical artery dissection (CAD) has been reported to be the sole most common cause, being responsible for up to 18 % of strokes (164). The pathophysiology and risk factors for CAD are incompletely understood, but since factors as diverse as high homocysteine levels, connective tissue disease, infection, manipulation of the neck and migraine are suggested to be CAD risk factors, it seems likely that CAD is a multifactorial disease (165).

Migraine has been demonstrated to be linked to CAD in several studies. In an early case-control study, 40 % of 50 CAD patients and 24 % of 100 controls reported a history of migraine (166). Tzourio *et al.* reported that 49 % of CAD patients and 21 % of control patients had a history of migraine (167). When migraine was divided into subgroups the difference was still significant among MO patients, but importantly not in MA subgroup. Recently Pezzini *et al.* evaluated the prevalence of migraine in 72 CAD patients and in control groups of similar size. The prevalence of migraine was over seven times higher in CAD patients than in healthy controls (OR 7,4 CI 95 % 3,1-17,6), but again there was no difference in prevalence of MA between the groups (168).

Certain pathophysiologically relevant genes have suggested links with migraine, CAD and IS. A methylenetetrahydrofolate reductase (*MTHFR*) polymorphism has been associated to MA (169), but conflicting results have also been reported (38, 39). Pezzini *et al.* linked both migraine and the C667T MTHFR genotype to CAD suggesting factors linking migraine and ischemic stroke (170). Furthermore, a large study reported that the same genotype in women with active MA increases risk for ischemic stroke more than fourfold (171).

6.1.5 Migrainous infarction (MI)

MI, according to the criteria of the ICHD-II is a rare condition (2) and the available clinical data are inadequate. Neurological deficit in a complicated migraine attack leading to MI should be similar to the aura in previous MA attacks and neuroradiological imaging should demonstrate an ischemic lesion in the corresponding region. In a study examining 2000 consecutive stroke patients during a 10-year period, only nine patients had MI according to the ICHD-II criteria for MI (172). Yet, they accounted for 14% of ischemic strokes in a subgroup of people younger than 45 years of age. In earlier studies, the incidence of MI has been estimated to be 0.8-3.36/100000/year (173) (174), but these studies have important methodological limitations as they were per-

formed before the ICHD-II criteria for MI and the exclusion of other etiological mechanisms has been insufficient.

MI appears to be more prevalent in women than in men (172, 175, 176). The most common location of the ischemia has been reported to be in the occipital lobe (175). However, the number of MI patients in some of these studies has been very low.

The pathophysiology of MI is still unknown. A potential mechanism is ischemia induced by cortical spreading depression, but other mechanisms, such as vessel wall alterations due to repeated arterial vasoconstrictions or hypercoagulability have been suggested (177).

6.1.6 MELAS and CADASIL

Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS) is a syndrome with neurological manifestations caused by mutations in the mitochondrial genome. Up to 77% of MELAS patients have reported a history of migraine or other headache (178). Mitochondrial dysfunction has been suggested to be part of migraine mechanisms (179) and increased amounts of fats and accumulations of subsarcolemmal or interfibrillar mitochondria in muscle biopsies have been reported in patients with migraine-related stroke (180). However, MO has not been associated with mitochondrial mutations (181).

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is the most common heritable cause of IS and vascular dementia. CADASIL is caused by mutations in the NOTCH3 gene in chromosome 19q12 (182). Up to 20-40% of CADASIL patients have MA and typically migraine is the first symptom of the disease beginning at the age of 30 (183).

6.2 Heart diseases

The reports of association between migraine and coronary heart disease (CHD) are conflicting, likely due to the several confounding factors between the two disorders. Preventive migraine treatments, such as beta-blockers and AT-II blockers, might decrease the prevalence of CHD in migraineurs as well as the use of aspirin in the acute treatment. Furthermore, CHD medications might alleviate migraine activity. On the other hand vasoconstricting agents, such as triptans, in acute treatment have been suspected to increase the possibility of ischemia, but this seems unlikely (62).

Kurth *et al.* evaluated the association of migraine and cardiovascular events in women and reported that women with active MA have approximately a twofold risk for both ischemic stroke and myocardial infarction (184). The authors also analyzed the impact of the overall cardiovascular risk pro-

file using the Framingham risk score. Interestingly in those women whose risk score was lowest the association of MA and ischemic stroke was highest (OR 3,88), whereas in those women whose risk score was highest the association of MA and myocardial infarction was highest (OR 3,34). Previously it has been reported that MA is associated with elevated risk of myocardial infarction (OR 2,1) in women and that MA is responsible for up to 18 major cardiovascular events per 10 000 women per year (149). Myocardial infarction is also associated to migraine in men (185). However, a meta-analysis by Schürks *et al.* found no association between migraine and myocardial infarction (147).

Mitral valve prolapse (MVP) is common valvular abnormality. Migraineurs are reported to have over two times higher risk for mitral valve prolapse (MVP) than controls (186).

6.3 Blood pressure

Studies on the association between migraine and blood pressure are controversial and there are some important confounding factors complicating its study. Several drugs used in migraine prophylaxis are primarily antihypertensive medications, such as beta-blockers and angiotensin II receptor blockers (129). On the other hand, headache is one of the clinical features of hypertensive encephalopathy.

Previously, migraine was typically associated with hypertension (187). For the most part, recent studies show links between migraine and hypotension as well as decreasing migraine activity with increasing blood pressure (188-190). A large population-based prospective study from Norway reported association between increasing pulse pressure and systolic blood pressure with decreasing prevalence of headache (191). Another study found association between decreased systolic and elevated diastolic blood pressure with migraine (192). On the other hand, patients with MA have been reported to have higher blood pressure than controls (193).

6.4 Epilepsy

Migraine and epilepsy share common clinical features, and therefore, the first publications about their association are over 100 years old. They are both paroxysmal disorders of the brain and patients are typically symptom-free between the attacks (194). Furthermore a loss of consciousness, the presence of auras, post-ictal drowsiness, aphasia and the possibility that attacks might be triggered by either visual or hormonal stimulus are all characteristics shared by both migraine and epilepsy as well as symptoms associated with gastrointestinal, psychological and autonomic nervous system conditions. Migraine attacks rarely trigger epileptic seizures, a phenomenon called migralepsy. Migraine-like headache can be associated with epileptic seizures, especially post-

ictally. Several antiepileptic treatments have been proven to work in migraine prophylaxis (see chapter 5.7).

On the population level prevalence of epilepsy has been estimated to be 0,5-1,0 %, but in migraine patients prevalence seems to be higher between 1,0 and up to 17,0 % (median 5,9 %) (195). Ottman *et al.* interviewed 1948 adult patients with epilepsy and 1411 of their family members. A history of migraine was reported by 24,4 % of epilepsy patients, by 23,0 % of family members with epilepsy and by 11,9 % of family members without epilepsy (196). The risk ratio for migraine was 2,4 (95 %, CI 2,02-2,89) in epilepsy patients compared to controls without epilepsy. The risk of migraine was increased in all subgroups of epilepsy patients, but surprisingly it was highest in the patients with epilepsy due to head trauma RR 4,1 (95 %, CI 2,92-5,70). Recently a Norwegian study found no association between migraine and epilepsy in a population-based study of 1656 participants, but still there was a trend toward comorbidity, especially among subjects with MA (197).

An Italian study evaluated the prevalence of epileptic seizures in 137 pediatric patients with different primary headache diagnoses and 10,2 % of these patients reported a history of seizures (198). Seizures were significantly more prevalent in MA patients (30,4 %) compared to patients with MO (4,8 %) and tension type headache (5,1 %). A study by Leniger *et al.* evaluated clinical characteristics of 61 patients with a comorbidity of migraine and epilepsy compared to 280 patients with epilepsy alone and 248 patients with migraine alone. A significantly larger proportion of comorbid patients had MA (41,0 %) than from patients with migraine without epileptic comorbidity (25,8 %) (199).

A population based case-control study, where migraine symptoms were evaluated, was carried out in Iceland with 145 cases with epileptic seizures and 188 controls. Migraine increased the risk for developing seizures almost fourfold (OR 3,7; 95 % CI 1,6-8,3), but importantly, association seemed to only be explained by MA patients in whom the OR was 8,2 (95 % CI, 2,3-28,9). In MO patients the OR was only 1,4 (95 % CI, 0,5-1,4) (200). Because MA commonly precedes seizures, the authors interpreted that MA seems to have a causative role in epilepsy. However, bidirectional comorbidity has been also suggested (201).

There are also some important differences between the diseases. The highest peak in incidence of migraine is in early adulthood, whereas in epilepsy peaks in both extreme ends of life. Furthermore the clear female preponderance in migraine prevalence is not evident among subjects with epilepsy.

Both migraine and epilepsy are paroxysmal brain disorders. They are believed to be a consequence of neuronal hyperexcitability. However, migraine seems to cause cortical spreading depression and epilepsy seems to cause hypersynchronous activity. Other

than rare forms of migraine and epilepsy, a few other episodic disorders such as long QT-syndrome and periodic paralysis are believed to be consequences of disturbances in ion transport molecules, so called channelopathies.

6.5 Other primary headaches

The prevalence of tension-type headache seems to be similar between MA, MO and non-migraineur controls, but the severity and frequency of tension-type headache is higher in subjects with migraine compared to controls (202, 203).

6.6 Psychiatric disorders

Already in the late forties Harold G. Wolff published his theory about the connection between psychiatric disorders and migraine. He explained the association with a so called "migraine personality". According to the theory, persons with migraine personality were delicate, shy, well-mannered, stubborn, inflexible, often had an undue attachment to their mothers in childhood and had generally been preoccupied with moralistic and ethical problems in adolescence, particularly with respect to sex. In adulthood, subjects were unusually ambitious, unable to relax, conscientious, perfectionist, meticulous, fastidious, poor at delegation, overanxious, tense at work and unable to cope with criticism.

The migraine personality theory is no longer mainstream, but the connection between migraine and depression has been shown in numerous cross-sectional and longitudinal studies. The first study to report the association in an unselected epidemiological setting was a study by Merikangas *et al.* (204). In the study, 457 young subjects from Switzerland were interviewed and migraine was significantly associated to depression (OR 2.2, 95% CI 1.1-4.8). Breslau *et al.* have reported in a longitudinal study that subjects with migraine have a three-fold higher risk becoming depressed and vice-versa, suggesting a bidirectional association and shared mechanism between these disorders (205, 206). However, conflicting results about the bidirectional nature of the association have also been reported (207). A similar bidirectional association has not been observed between depression and other severe headaches other than migraine, even though severe headache increases the risk of depression (206). The risk of depression seems to increase with increases in the frequency of migraine headache (208), but depression does not have an impact on the prognosis of migraine (206). It seems depression has a stronger link to MA than MO (209), especially in women (210).

The nature of the association of these conditions is still only speculation. Chronic painful diseases and unpredictable painful and disabling attacks may naturally stir thoughts of helplessness, anger and frustration

that lead to depression and/or anxiety. On the other hand, migraine and chronic headache may be though of as a somatic manifestation of depression. However, migraineurs seem to have a higher risk of depression and anxiety than subjects with other chronic pain disorders such as arthritis and back pain (211), suggesting biological and shared mecnism.

Migraineurs have been reported to have almost four times higher risk for generalized anxiety disorder (GAD) than controls (211). GAD subjects with migraine have been reported to have a higher risk for social phobia (204) and panic disorder (212). Subjects with migraine and anxiety have been reported to have an extremely high risk for depression (OR 22.8, CI 95% 12.7-41.2) (213).

Bipolar disorder is also associated to migraine. Migraineurs are reported to have higher risk for bipolar disorder than controls (8.8% vs. 3.3%) (204) and subjects with bipolar disorder are reported to have a higher prevalence of migraine than controls (24.8% vs. 10.3.%) (214)

6.7 Immunological diseases

6.7.1 Multiple sclerosis

According to different studies, lifetime prevalence of headache in patients with multiple sclerosis (MS) varies between 4 % and 58 % (215). Zorzon *et al.* reported in a case-control study that migraine is an independent risk factor for MS (OR 13,5, 95 % CI 1,5-116,6) (216). Another study showed a stronger association of migraine with relapsing-remitting MS (50,9 %) than progressive MS (18,7 %) (215). However, in a recent large-scale study there was no difference in the prevalence of migraine between patients with MS and healthy controls (217). Lifetime prevalence of migraine in MS patients has been estimated to be 16 % (218).

6.7.2 Allergy and asthma

Migraine patients are often aware of how specific foods may act as triggering factors for a migraine attack. The first reports associating migraine and allergy are from the 1800s. In 1927 Vaughn found ten migraine patients with food triggers and showed that 36,4 % (12/33) of his migraine patients have an allergy triggering migraine attacks. In the 1950s, Unger *et al.* concluded that migraine is probably an allergic disease because of the excellent relief of migraine symptoms by avoiding triggering nutritional factors (219). The most common foods reported to cause migraine symptoms are wheat, orange, eggs, tea, coffee, chocolate, milk, beef, corn, cane sugar and yeast (220).

Patients with allergic rhinitis are reported to have a higher prevalence of migraine than controls (81) and migraineurs have been reported to have el-

evated plasma IgE and histamine levels (221). Histamine levels are also elevated during migraine attacks compared to inter-ictal levels of the same individuals (222). Nevertheless anti-allergic and anti-asthmatic medications, such as montelukast and antihistamine have not been shown to be effective in migraine prophylaxis (223, 224).

Migraine is associated with elevated risk of asthma (225). Aamodt *et al.* reported in the large Norwegian Head-HUNT study that patients with asthma had a 1,5 times higher risk of migraine. Furthermore the study demonstrated that the risk of asthma increases with migraine frequency (226).

6.8 Gastrointestinal disorders

Investigation of the association between migraine and gastrointestinal disorders has several limitations or problems. Sometimes, and especially in children it is difficult to interpret whether gastrointestinal symptoms are reflecting independent disorders or whether they are part of the migraine cascade. Of the pediatric population, 4,1 % fulfill the criteria of abdominal migraine (227), and although much more rare, it also appears in the adult population (228). Symptoms or disorders like gastric ulcer, may be side-effects of migraine medications, such as aspirin, rather than independent disorders.

Kurth *et al.* evaluated the prevalence of abdominal symptoms in migraineurs and observed that 80,9% of migraine patients had had upper abdominal pain during previous 12 months compared to 37,5% of controls. Importantly, the difference was stronger among non-aspirin users compared to aspirin users (229). Elevated prevalence of abdominal pain was also reported among migraineurs compared to controls in a large Finnish study of school children (230). An Italian study suggests association of helicobacter pylori with migraine and even points out possible alleviation of headache symptoms after eradication of the bacteria (231). However, subsequent studies on the subject have been controversial (232-234).

AIMS OF THE STUDY

The aims of the study were:

• To study the comorbidity of migraine and its subtypes with other diseases such as epilepsy, allergy, psychiatric disorders, ischemic stroke and cervical artery dissection. (Studies I, III)

• To identify loci predisposing to migraine aura. (Study II)

• To compare clinical characteristics of migraine in both patients with dissection and healthy controls. Furthermore the aim was to analyze effect of dissection to the activity of migraine. (Study III)

• To evaluate the efficacy and tolerability of triptans in the acute treatment of rare migraine with aura variants suffering hemiplegic migraine. (Study IV)

SUBJECTS

The Finnish Migraine Gene Project (I, II and IV)

Patients of studies I, II and IV were obtained from the Finnish Migraine Gene Project (FMGP) for which migraine families have been collected nation-wide since 1992. The patients were recruited from seven headache outpatient neurology clinics nation-wide (Helsinki, Kemi, Turku, Jyväskylä, Mikkeli, Tampere, and Seinäjoki) (235). When a member of a family, the index case, was clinically diagnosed by a neurologist as suffering from migraine, the index case was asked to contact all other migraineurs in the family to ask if they would also be willing to participate in the study. If at least three possible migraine sufferers were willing to participate from the family, a validated questionnaire, the Finnish Migraine Specific Questionnaire for Family Studies (FMSQFS) was mailed to each of them as well as to their parents and siblings (236). All participants gave their informed consent. The study was approved by the local ethics committee in Helsinki University Central Hospital.

The FMGP included, at the time of the present study, 7496 individuals (63.3% women) from 1618 families. Data was sufficient for diagnostic evaluation in 7225 subjects of which 4967 (68.7%) were migraineurs (table 9). For each participant the fulfilment of the current migraine criteria of the International Headache Society was assessed. 2496 participants had MA and 4623 had MO according to the ICHD-II. Most migraineurs were women, 75.8 % in the MA and 73.8% in the MO groups.

Cervical artery dissection database (III)

Cervical artery dissection (CAD) is a common cause of ischemic stroke in young adults. The CAD database consists of all 346 verified CAD patients (aged ≥15) without subarachnoidal hemorrhage treated at the Helsinki University Central Hospital from January 1994 to December 2008. All participants gave their informed consent. The study was approved by the local ethics committee in Helsinki University Central Hospital.

Table 9. Distribution of the different diagnoses in the Finnish Migraine Gene Project

	ALL	WOMEN (%)
Migraine	4967	3640 (73.4%)
Migraine with aura	2496	1892 (75.8%)
Migraine without aura	4623	3414 (73.8%)
No migraine	2258	958 (42.4%)
All	7225	4624 (64.0%)

Patients

Study I

Study I includes 1000 consecutive participants from the FMGP that belong to 251 families (Table 10). Comorbidities were evaluated in 678 family-members with migraine and in 322 family-members without migraine. Two subjects were excluded from the study because they did not report their medical conditions.

Study II

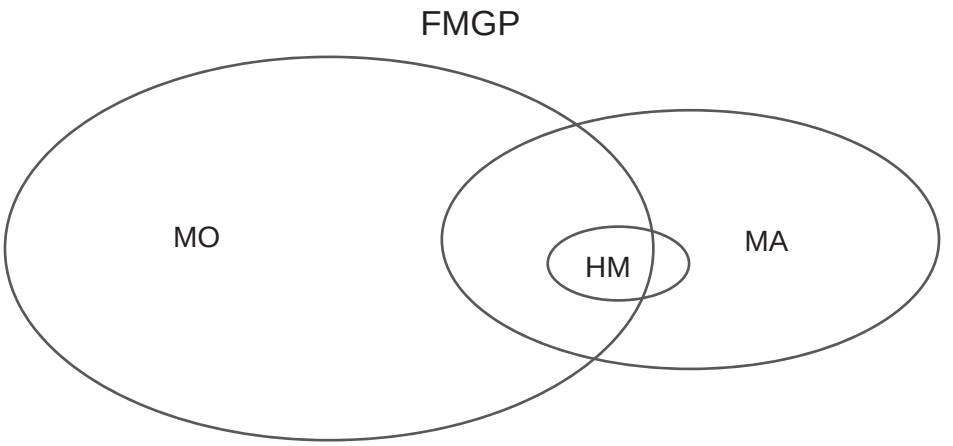
Families in study II were selected from the FMGP based on the high prevalence of visual aura symptoms and the fulfilment of the IHS criteria for typical MA. The study sample consisted of 351 subjects (224 women and 127 men) from 36 families.

Study III

Of the 346 patients in the CAD database, 313 were included in the study. Thirty-three patients were excluded, because information regarding migraine was missing: seven had died; four had severe aphasia; five were at nursing homes; and 17 patients could not be reached or refused to participate in the study. Controls, frequency-matched by 5-year age intervals and sex within the CAD-group, were recruited randomly with the help of the Finnish Population Register Center from the population living in the catchment area of our hospital.

Study IV

At the time of analysis, the FMGP included 5351 subjects (61.9% women) of which 3389 (63.3%) were migraineurs. The database included 198 subjects with hemiparesis as a part of their migraine aura. All 76 subjects with hemiplegic migraine who had used triptans at least once in the treatment of migraine were included in study IV.



MA=Migraine with aura
MO=Migraine without aura
HM=Hemiplegic migraine

Figure 6. Illustration of the distribution of migraine diagnoses in the Finnish Migraine Gene Project (FMGP).

Table 10. Study populations and subjects in studies I-IV.

STUDY	STUDY POPULATION	CASES	CONTROLS
I	1000 consecutive participants in the FMGP	676 family members with migraine	322 family members without migraine
II	Members of 36 consecutive families with high prevalence of MA from the FMGP	185 subjects with ICHD-II aura	166 subjects without ICHD-II aura
III	346 subjects from the CAD database	313 CAD patients	313 healthy controls
IV	198 family members with HM from FMGP	76 family members with HM and triptan use	Controls not used

FMGP=Finnish Migraine Gene Project
MA=Migraine with aura
ICHD-II=International Classification for Headache Disorders, 2nd edition
CAD=Cervical Artery Dissection
CAD database=All CAD patients (aged ≥15) treated at Helsinki University Central Hospital from January 1994 to December 2008
HM=Hemiplegic migraine

METHODS

Questionnaire (I-IV)

Clinical data from the study participants was collected using the validated questionnaire FMSQFS. The FMSQFS includes precise questions concerning characteristics of migraine, such as, activity, comorbidity, hereditability, triggering factors, aura symptoms and treatment of migraine (236). The FMSQFS divides subjects into the following ICHD-II based diagnostic categories: migraine aura without headache (ie. migraine equivalents, EQV); MA; migraine attacks fulfilling the criteria of both migraine with and without aura (MA+MO); migraine with aura not fulfilling all the current criteria (UNC); MO; headache other than migraine (HA); and no headache (NO).

The comorbidity of migraine was studied by evaluating the medical illnesses reported in the FMSQFS. Table 11 presents the wording (translated into English) concerning these illnesses in the questionnaire. Family-members with migraine were compared to family-members without migraine. Differences between migraine subgroups were noted as well. All comorbidities reported by the patients were noted and the following were chosen for closer study: epilepsy, stroke, hypertension, hypotension, allergy and psychiatric disorders. Definition of hypotension was a blood pressure lower than 115/70 mmHg.

In study IV, subjects were selected from the FMGP database. Those patients who reported hemiparesis as a part of their migraine aura in FMSQFS (236) were systemically interviewed by a research-neurologist (V.A) to confirm the diagnosis HM. The subjects were asked precise questions concerning visual, sensory, motor, dysphasic and basilar-type aura symptoms, and their frequency, severity, location, gradual development, sequence, length and age at onset. All diagnoses were based on the ICHD-II (2) and the individuals who fulfilled the criteria for both FHM and SHM and those who had used triptans at least once as an abortive treatment of migraine were included in study.

The efficacy of the triptans and treatment-related adverse events were rated on a scale from 0 to 10 (no response or side effects 0, excellent response or unbearable side effects 10). In addition, subjects reported how many occasions they had used triptans and during which phase of a migraine attack (i.e. aura or headache) the medication had been taken.

Genotyping (II)

DNA from the patients' blood samples was extracted using either the standard phenol-chloroform extraction procedure or the Autopure LS automated purification instrument (Gentra Sys-

Table 11. Wording used in the FMSQFS concerning illnesses of participants

Previous illnesses:	
Do you have or have you had:	
- Stroke (or cerebral infarction)	( )
- Intracerebral haemorrhage	( )
- Other cerebral circulatory disorder of what kind:.....……	( )
- Epilepsy	( )
- Seizure	( )
- Fit of unconsciousness	( )
- Fever convulsion as a child	( )
- Hypertension	( )
- Myocardial infarction	( )
- Symptomatic heart disease	( )
- Cardiac insufficiency	( )
- Atrial fibrillation	( )
- Other cardiac arrhythmia	( )
- Ménièr's disease	( )
- Eye disease which:.....	( )
- Diabetes which:	( )
- Cancer which:.....	( )
- Rheumatic condition which:.....	( )
- Allergy or atopy: which one:	( )
- Mental disorder	( )
Depression, severe depression	( )
Anxiety disorder that needed treatment	( )
Panic disorder	( )
Insomnia	( )
Other, which:.....……	( )
- High cholesterol level	( )
- High triglyceride level	( )
- Do you have or have you had some other significant illness: which:.....	( )
None of the above	( )
- Your latest blood pressure value was ..... / ..... mmHg (systolic / diastolic)	
- You do not remember but you were told it was or has been:	( )
High ( ) Low ( ) Normal ( )	

FMSQFS=Finnish Migraine Specific Questionnaire for Family Studies

tems, Minneapolis, USA). Genotyping of the DNA-samples was based on the LMS-MD10 microsatellite marker set (Applied Biosystems, Foster City, CA, USA) of 378 markers, with an average marker distance of 10 cM and performed using the ABI 3730 capillary sequencing instrument as described by Anttila et. al. (51). For fine-mapping, eleven additional markers on chromosome 9q21-q31 were selected using the location, heterozygosity and primer information provided by the UCSC database (http://genome.ucsc.edu/).

Cervical artery dissection database (III)

Potential subjects for study III were identified using a search of the Helsinki University Central Hospital's databases for diagnoses related to CAD and stroke. The medical records of individuals diagnosed were reviewed by stroke neurologists. Radiological images of patients in whom CAD was considered possible were re-analyzed by an experienced neuroradiologist. In uncertain cases, the patient was excluded. All patients included in the study displayed one or more of the typical diagnostic radiological characteristics. Patients presenting with subarachnoid hemorrhage (SAH) were treated in a neurosurgical unit and were not included in the present study. There were 233 patients who were re-interviewed to fill in missing data.

Both CAD patients and healthy controls were semistructurally interviewed by a research neurologist (V.A., T.M.M.) and lifetime prevalence of migraine and its subtypes were evaluated in both study groups. Migraine was diagnosed based on the ICHD-II classification criteria (2). Data on migraine characteristics were collected using the FMSQFS (236). The evaluated features were migraine severity (mean age at onset of migraine, vomiting, typical length of attack and total number of moderate or severe attacks) and possible vascular properties of migraine (Raynaud phenomenon, prodromal neck sensations and pulsating nature of headache). Characteristics of CAD were compared between migraineurs and non-migraineurs. Furthermore, use of oral contraceptives and smoking were evaluated in both groups.

To study the effect of CAD on migraine, the patients were asked whether the activity of migraine had changed after CAD using the following scale: i) complete alleviation of migraine, ii) marked alleviation of migraine, iii) slight alleviation of migraine, iv) no influence, v) slight increase, and vi) marked increase in migraine activity.

Statistics

The data were recorded and analysed using the Statview 5.0 software package (Abacus Concepts, Inc., Berkley, CA, USA, 1996). Parametric test (T-test), Chi-square and Fisher's Exact test were applied when appropriate. Non-continuous data was analyzed with the Mann-Whitney U test.

A two-tailed value of $P \leq 0.05$ was considered statistically significant. Odds ratios (ORs) and 95% confidence intervals were calculated by Binominal Logistic Regression Models with CAD and control groups as outcome variables, controlling for age, sex, hypertension, current smoking, and diabetes.

Two-point parametric linkage analysis was performed using the LINKAGE (237) and HOMOG (238) programs. Affected-sib-pair (ASP) analysis was performed to investigate the possibility of recessive inheritance. For regions showing evidence of linkage in the parametric two-point analysis, multipoint non-parametric analysis was performed using the SimWalk program (239). In the analyses, an affecteds-only strategy was applied, and thus, only individuals fulfilling the diagnostic criteria of aura were treated as affecteds and all other individuals were set to unknown. A Lod Score under locus heterogeneity (LodHet) of 3.3 was considered significant evidence of linkage (240). LodHet thresholds of 1.9 were used to identify suggestive evidence of linkage.

Table 12. Methods used in studies I-IV

STUDY	METHODS
I	FMSQFS
II	FMSQFS + genome-wide linkage analysis
III	FMSQFS + semistructural interview
IV	FMSQFS + semistructural interview

FMSQFS=Finnish Migraine Specific Questionnaire for Family Studies

7 Migraineurs have an elevated risk for hypotension, allergy and psychiatric disorders (I)

The 1000 participants of this study belonged to 251 separate families. 60.6% (606 individuals) were women and 39.4% men. The mean ages were 40.0 years among all participants, 40.8 years in women, 38.8 years in men. 678 participants had migraine, 70.5% of the migraineours were women (478 individuals) and 29.5% (200 individuals) men. Of the migraineurs 16 patients were diagnosed with EQV, 226 with MA+MO, 140 with MA, 144 with UNC and 152 with MO. The mean age of the migraine patients was 38.5 years (39.6 years for women and 36.0 years for men). The mean age of the family members not affected by migraine was 43.1 years (45.4 years for women and 41.6 for men). Two participants did not report their medical illnesses and 43 did not report their blood pressure.

Table 13. Comorbidities in family members with migraine compared to family members without migraine

COMORBIDITY STUDIED	FAMILY MEMBERS WITHOUT MIGRAINE	FAMILY MEMBERS WITH MIGRAINE	
	N=676	N=322	
	%	%	OR (95% CI)
Epilepsy	4,1	2,9	1.38 (0.64-2.97)
Women	3,1	3,4	0.76 (0.27-2.15)
Men	6,1	2,4	2.84 (0.89-9.04)
Stroke	2,5	1,6	1.74 (0.66-4.60)
Women	2,5	2,2	1.36 (0.37-5.10)
Men	2,5	1,3	2.39 (0.48-11.73)
Hypertension	11,8	11,6	1.11 (0.71-1.73)
Women	11,5	11,3	1.25 (0.65-2.39)
Men	12,1	11,5	1.12 (0.57-2.18)
Hypotension	26,0	20,7	1.43 (1.02-2.01)
Women	32,1	30,8	1.32 (0.83-2.09)
Men	10,7	16,3	0.64 (0.32-1.14)
Allergy	34,0	22,0	1.83 (1.34-2.51)
Women	37,4	22,0	2.01 (1.26-3.19)
Men	25,4	22,2	1.18 (0.73-1.92)
Psychiatric disorder	11,1	2,9	4.09 (2.11-7.92)
Women	12,9	5,6	2.82 (1.28-6.19)
Men	5,1	1,3	3.90 (1.03-14.67)

CI = Confidence Interval
OR = Odds Ratio

Distribution of comorbidities is shown in Table 13 between participants with and without migraine. Migraine patients statistically significantly reported more hypotension (OR 1.43; CI 95% 1.02-2.01), allergy (OR 1.83; CI 95% 1.34-2.51) and psychiatric disorders (OR 4.09; CI 95% 2.11-7.92) compared with their family members without migraine. Differences regarding epilepsy, stroke and hypertension were not statistically significant.

Table 14 presents reported comorbidities in the different diagnostic categories of the study. The MA, MA+MO and UNC groups reported significantly more allergy and psychiatric disorders compared to the NO category. The corresponding OR's were as follows: MA 1.68 (CI 95% 1.01-2.79) for allergy and 3.46 (CI 95% 1.17-10.21) for psychiatric disorders; MA+MO 1.86 (CI 95% 1.17-2.97) for allergy and 5.91 (CI 95% 2.16-16.20) for psychiatric disorders; and UNC 1.68 (CI 95% 1.02-2.78) for allergy and 5.21 (CI 95% 1.80-15.05) for psychiatric disorders.

Additionally, subgroup analysis showed that women with MA+MO reported more hypotension (OR 2.12; CI 95% 1.065-4.23) than women in the NO group and men with MA+MO reported more epilepsy (OR 6.76; CI 95% 1.028-44.48) and stroke (OR 15.19; CI 95% 1.15-200.88) than men in the NO group. Epilepsy was also more prevalent among men with UNC (OR 5.88; CI 95% 1.063-32.57) compared to men in the NO group. There were no significant differences between MO and NO groups or between EQV and NO groups.

Table 14. Comorbidites in family members with different study diagnoses in the Finnish migraine families

COMORBIDITY STUDIED	EQV	MA	MA+MO	UNC	MO	HA	NO	CATEGORIES SIGNIFICANTLY DIFFERENT FROM NO
	N=16	N=140	N=224	N=144	N=152	N=116	N=206	
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	OR (95% CI)
Epilepsy	0,0	5,0	4,5	4,2	3,3	4,3	1,9	none
Women (N=20)	0,0	6,4	3,7	1,0	1,1	5,2	2,9	none
Men (N=17)	0,0	2,2	8,1	11,1	6,3	3,4	1,5	MA+MO 6.76 (1.028-44.48) UNC 5.88 (1.063-32.57)
Stroke	2,2	2,1	3,6	2,1	0,7	2,6	1,5	none
Women (N=15)	11,1	2,1	3,2	2,0	1,1	1,7	2,9	none
Men (N=7)	0,0	2,2	5,4	2,2	0,0	3,4	0,7	MA+MO 15.19 (1.15-200.88)
Hypertension	12,5	10,0	11,6	11,1	9,9	7,8	18,0	none
Women (N=72)	11,1	9,6	11,2	14,1	7,9	10,3	20,0	none
Men (N=47)	14,3	10,9	13,5	4,4	12,7	5,2	16,9	none
Hypotension	12,5	22,8	32,3	26,8	23,0	25,2	16,0	none
Women (N=186)	22,2	30,4	37,3	33,0	27,7	31,6	20,9	MA+MO 2.12 (1.065-4.23)
Men (N=47)	0,0	6,8	7,9	12,2	16,1	18,5	13,4	none
Allergy	18,8	33,6	39,7	36,8	28,3	22,4	20,9	MA 1.68 (1.01-2.79) MA+MO 1.86 (1.17-2.97) UNC 1.68 (1.02-2.78)
Women (N=212)	11,1	37,2	41,2	38,4	36,0	25,9	20,0	MA 2.48 (1.18-5.23) MA+MO 2.67 (1.35-5.28) UNC 2.36 (1.13-4.95)
Men (N=92)	28,6	26,1	32,4	33,3	17,5	19,0	21,3	none
Psychiatric disorder	6,3	9,3	14,7	11,8	5,9	5,2	2,4	MA 3.46 (1.17-10.21) MA+MO 5.91 (2.16-16.20) UNC 5.21 (1.80-15.05)
Women (N=71)	0,0	11,7	17,6	14,1	5,6	10,3	2,9	MA 5.37 (1.13-25.49) MA+MO 10.16 (2.30-44.82) UNC 7.65 (1.64-35.76)
Men (N=13)	14,3	4,3	0,0	6,7	6,3	0,0	2,2	none

CI = Confidence Interval; OR = Odds Ratio; MA=migraine with aura; MO=migraine without aura; UNC=unclassified migraine; HA=headache; NO=no headache

8 A visual migraine aura locus maps to 9q21-q22, a known occipitotemporal lobe epilepsy locus (II)

The study sample consisted of 36 families and 351 (224 women and 127 men) individuals. The mean number of MA affected individuals per family was 5 and the average family size was 15 individuals in three generations. The distribution of migraine diagnoses is shown in Table 15. Of the 351 genotyped individuals, 245 had migraine according to the ICHD-II criteria. Among this group, 185 (52%) had aura fulfilling the ICHD-II criteria, 25 had non-ICHD-II aura and 35 had no aura at all while having ICHD-II headache (i.e. they had pure MO). Table 15 summarises the aura and headache characteristics of the study population.

Table 15. Phenotypes of the genotyped individuals categorized by aura symptoms

MIGRAINE AURA	HEADACHE	N	% FEMALE
ICHD-II-aura	Migraine headache	160 [d]	79.4
	Probable migraine headache [c]	13	46.2
	Non-migraine headache	8	25.0
	No headache	4 [e]	25.0
Total (ICHD-II-aura)[a]		185	73.5
Unclassified aura	Migraine headache	25	72.0
	Probable migraine headache [c]	5	60.0
	Non-migraine headache	3	100.0
	No headache	1	100.0
Total (Unclassified aura)[b]		34	73.5
No aura	Migraine headache	35 [f]	60.0
	Probable migraine headache [c]	28	42.9
	Non-migraine headache	12	58.3
	No headache	48	37.5
Total (No aura)		123	47.2
Missing diagnosis	Missing diagnosis	9	55.6

[a] Total number of individuals having aura fulfilling ICHD-II criteria of migraine aura but the migraine headache does not necessarily fulfil the ICHD-II criteria
[b] Total number of individuals with unclassified aura refers to patients that are suffering from aural features that do not fulfil all ICHD-II criteria for migraine aura. The migraine headache also does not necessarily fulfil ICHD-II criteria
[c] Probable migraine refers to patients with episodic headaches with some migraineous features that do not fulfil ICHD-II criteria for migraine without aura
[d] Number of individuals with the end diagnosis of migraine with aura
[e] Number of individuals having migraine aura without headache, i.e. equivalent migraine
[f] Number of individuals with the end diagnosis of migraine without aura

Table 16. Distribution of different aura symptoms in 185 subjects with ICHD-II aura

SCINTILLATING SCOTOMA	HOMONYMIC HEMIANOPIA	SPEECH DISTURBANCES	HEMIPARESIS
86%	69%	41%	25%

All subjects with ICHD-II-aura had visual aura (scintillating scotoma, homonymic hemianopia or both) (table 16.). A remarkably large proportion of subjects reported motor symptoms or speech disturbances beyond their visual symptoms as a part of their aura, but only occasionally (table 16).

The parametric two-point linkage analysis showed significant evidence of linkage (LodHet=4.67) between migraine aura and a locus on 9q31 (D9S1690 at 104.1 cM). Further evidence of linkage to four other markers surrounding D9S1690 was detected in the ASP analysis. The summary plots of both parametric two-point LodHet scores and non-parametric ASP values for chromosomes 1-22 and X are shown in figure 7. Non-parametric multi-point analysis indicated significant evidence of linkage ($p<0.01$) between 9q22-q31 and migraine aura, supporting the evidence of a visual aura locus on 9q21-q31.

The highest linkage signal was detected when all individuals with aura, including those having aura without headache, were considered affected (table 17). Significant but reduced evidence of linkage (LodHet 4.31) was observed when subjects with both the headache and aura were analysed. When all the 220 individuals fulfilling the IHS criteria for migraine headache were considered as affecteds (including the 160 individuals with the MA end-diagnosis), the linkage signal was inflated by 1.8 units (to suggestive evidence of linkage, LodHet 2.91).

Table 17. Lod scores in different end-diagnoses

ANALYZED PHENOTYPES	LODHET	N
Subjects with ICHD-II-aura[a]	4.7	185
Subjects with MA[b]	4.3	160
Subjects with migraine headache[c]	2.9	220

[a] *All subjects fulfilling ICHD-II criteria of migraine aura (with or without headache)*
[b] *All subjects fulfilling ICHD-II criteria of MA*
[c] *All subjects fulfilling ICHD-II criteria of migraine headache (with or without aura)*

To increase the linkage information and to further narrow the susceptibility locus, eleven additional microsatellite markers were genotyped in the linked region extending from 85 cM to 124 cM with a mean map distance of 2.7 cM. When those markers were included with the original markers in the non-parametric multi-point linkage analyses, the highest linkage signal modelling dominant inheritance was found at 94.7 cM (pdom=0.0003), approximately 10 cM proximal from the best marker (D9S1690) identified in the two-point linkage analysis. Sex-specific, two-point parametric linkage analysis for chromosome 9 did not improve the linkage signal.

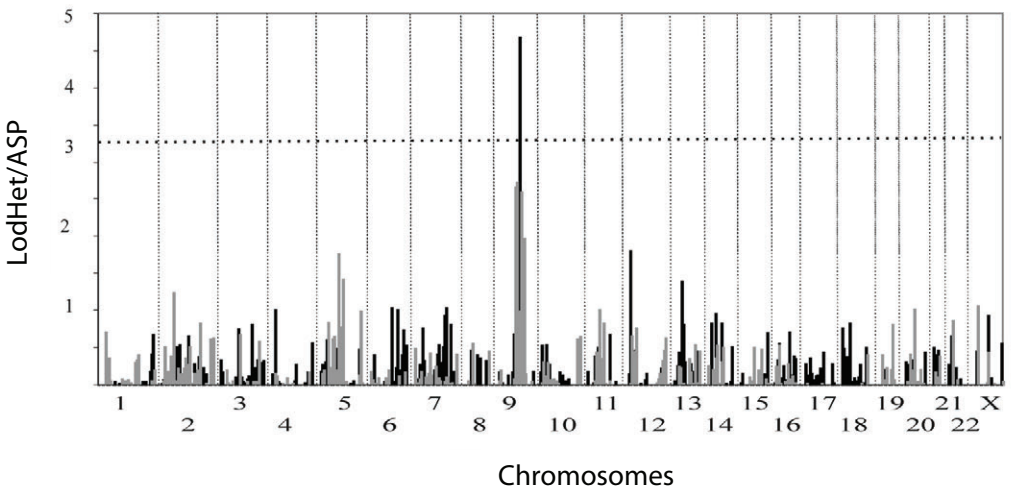


Figure 7. Results of the genome-wide linkage analyses for visual migraine aura. Plots of parametric (black bars) and non-parametric (grey bars) two-point linkage analysis for chromosomes 1-22 and X. The dotted horizontal line shows the significance threshold in HLOD.

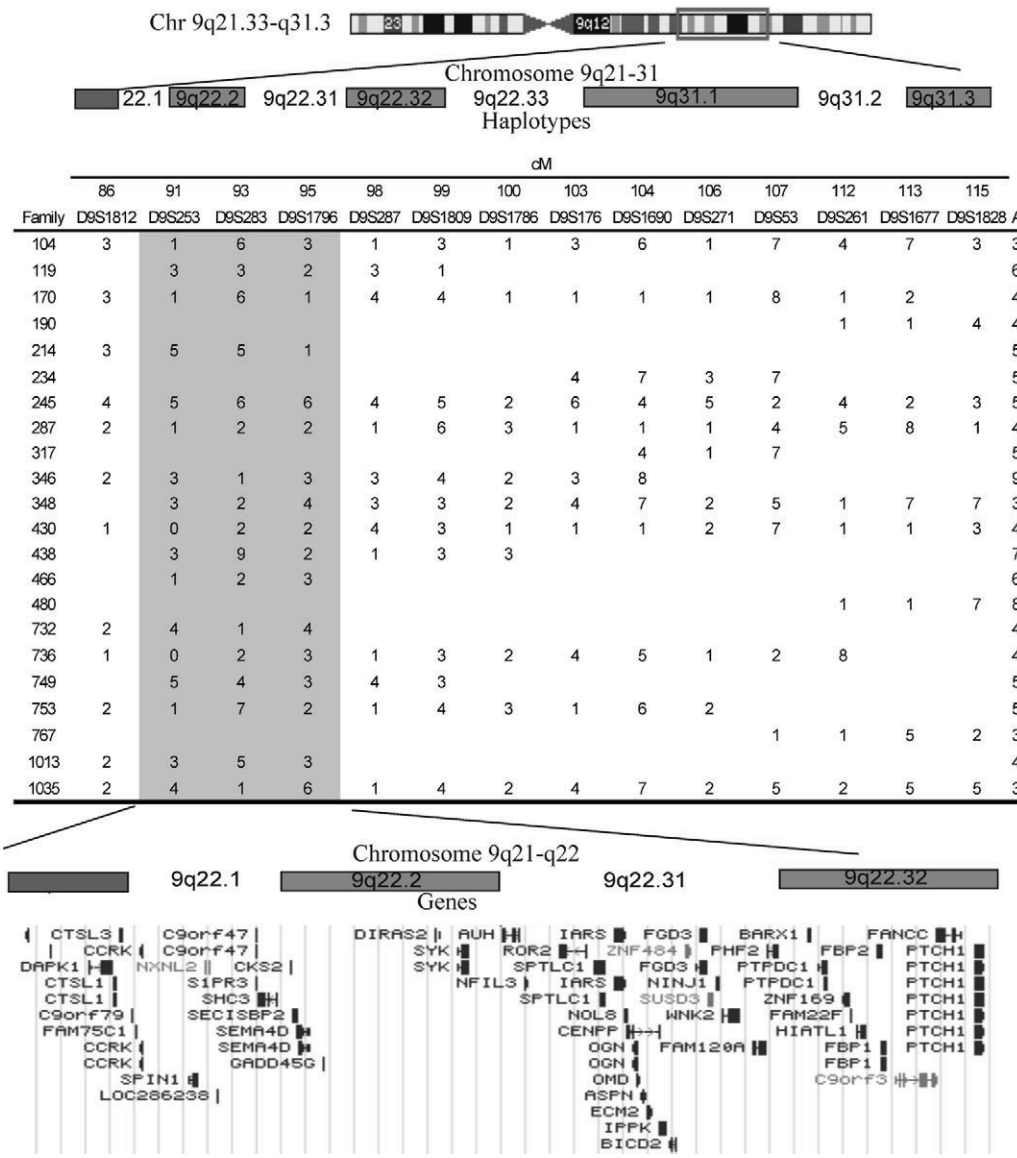


Figure 8. Family-specific haplotypes shared by all or almost all of the affecteds in the 22 families that showed evidence of linkage in the 9q21–q31 region. Marker positions (cM) are based on the deCODE genetic map. The grey area, including the markers D9S253, D9S283 and D9S1796, indicates the extent of the shared region in 17 of the 22 families. This refined linkage region extends from 86 to 98 cM and covers 9.8 Mb. The last column, labeled "aura", lists the proportion of affecteds with the shared haplotype, excluding married-in spouses. The bottom of the figure shows the genes in the region as presented by the UCSC database (March 2006 assembly).

To further restrict the linked region and to identify the susceptibility gene, a haplotype analysis was performed (figure 8). The 22 families that had a family-based linkage score above 0.3 (SimWalk dominant statistics pdom<0.5) at and around the highest linkage location were analyzed. These families contained 208 genotyped individuals of which 106 are considered affected with visual aura. In 17 out of these 22 families, affected individuals shared a family-specific haplotype between the markers D9S253-D9S1796 from approximately 86 cM to 98 cM. The haplotype region was restricted on both sides due to recombinations in eight families.

In addition to chromosome 9, the ASP analysis found suggestive evidence of linkage between migraine aura and 5q13 (ASP Lod 1.8 at 91 cM). Parametric analysis found nearly suggestive evidence of linkage to 12p13 (HLOD 1.8 at 15 cM).

9 Migraine with aura is a risk factor for cervical artery dissection (III)

Of the 313 consecutive CAD patients (105 women and 208 men), 288 (92.0%) had uniarterial and 25 (8.0%) had two-vessel CADs. The mean age at CAD onset was 46.1 years (range 15 to 78, median 45) (table 18). The mean age of controls was 45.8 years (range 21 to 74, median 45, P=0.79). Among CAD patients, male preponderance was observed (66.5%, P<0.001). Smoking was more common among subjects with CAD than in controls (36.7% vs. 22.7%, P<0.001). Hypertension was more prevalent among subjects with CAD than in controls (42.1% vs. 24.0, P<0.001). Current oral contraceptive use occurred in 36.2% of female CAD patients and in 24.8% of healthy female controls (P=0.072). There was difference in prevalence of diabetes between studied groups (3.8% vs. 6.7%).

Table 18. Demographic and migraine related features of subjects with CAD and controls

	DISSECTIONS	CONTROLS	P VALUE
Mean age (y)	46.1	45.8	0.79
Women (%)	105/313 (33.5)	105/313 (33.5)	1.0
Current smoking (%)	115/313 (36.7)	71/313 (22.7)	<0.001
Hypertension (%)	129/313 (41.2)	75/313 (24.0)	<0.001
Diabetes (%)	12/313 (3.8)	21/313 (6.7)	0.11
Oral contraceptives (% of women)	38/105 (36.2)	26/105 (24.8)	0.072

Migraine and especially MA were more common among CAD patients than in controls (Table 19.). Accordingly, migraine prevalence was 36% (114/313) for CAD patients and 23% (71/313) for controls (OR 2.15; 95% CI 1.48-3.14), while 23% (71/313) of CAD patients and 12% (39/313) of controls had MA (OR 2.41; 95% CI 1.53-3.80). Percentages and adjusted ORs of reported migraine history and MA in CAD patients and in controls presented separately for both genders were as follows: for women; migraine 54% (57/105) vs. 35% (37/105) (OR 2.30; 95% CI 1.28-4.13), MA 35% (37/105) vs. 18% (19/105) (OR 2.79; 95% CI 1.40-5.59); for men; migraine 27% (57/208) vs. 16% (34/208) (OR 2.02; 95% CI 1.23-3.31), MA 16% (34/208) vs. 10% (20/208) (OR 2.21; 95% CI 1.19-4.11). There were no differences in prevalence of MO between CAD patients and controls.

Table 19. Lifetime prevalence of migraine in patients with cervical artery dissection (n=313) and healthy controls (n=313). Odds Ratios are adjusted for age, sex, oral contraceptives, hypertension, diabetes and current smoking.

	DISSECTIONS (%)	CONTROLS (%)	ADJUSTED OR	95% CI
All				
Migraine	114/313 (36)	71/313 (23)	2.15	1.48-3.14
Migraine with aura	71/313 (23)	39/313 (12)	2.41	1.53-3.80
Migraine without aura	43 (14)	32/313 (10)	1.64	0.98-2.76
Women				
Migraine	57/105 (54)	37/105 (35)	2.30	1.28-4.13
Migraine with aura	37/105 (35)	19/105 (18)	2.79	1.40-5.59
Migraine without aura	20/105 (19)	18/105 (17)	1.60	0.74-3.49
Men				
Migraine	57/208 (27)	34/208 (16)	2.02	1.23-3.31
Migraine with aura	34/208 (16)	20/208 (10)	2.21	1.19-4.11
Migraine without aura	23/208 (11)	14/208 (7)	1.75	0.84-3.65

Table 20. Features of CAD in subjects with and without migraine

	MIGRAINE (%)	NON-MIGRAINE (%)	P VALUE
Vertebrobasilar dissection	56/114 (49)	92/199 (46)	0.62
Bilateral dissection	9/114 (8)	16/199 (8)	0.94
Occlusion	48/114 (42)	87/199 (44)	0.85
NIHSS at onset	3.3	4.4	0.30
Rankin at 3 months	1.1	1.3	018
Intracranial dissection	32/114 (28)	59/199 (30)	0.77
Ischemic stroke	77/114 (67)	144/199 (72)	0.37

NIHSS=National Institutes of Health Stroke Scale

71% percent (223/313) of all CAD patients suffered from ischemic stroke. No difference in the incidence of brain infarct between migraineurs (67%) and non-migraineurs (72%) was apparent (table 20). Neither were the differences between migraineurs and non-migraineurs when considering whether the affected arteries were bilateral (8% vs. 8%), intracranial (28% vs. 30%), vertebrobasilar (49% vs. 46%) or had occlusion caused by a dissected artery (42% vs. 44%). Furthermore, the severity of neurological deficits at onset according to the National Institutes of Health Stroke Scale (median 1.5 vs. 2.0; mean 3.3 vs. 4.4, P=0.27) and the outcome at three months on the modified Rankin Scale (median 1.0 vs. 1.0; mean 1.1 vs. 1.3, P=0.20) were similar between patients with and without migraine.

Other variables lacking significant correlation were severity and vascular features of migraine between subjects with CAD and controls (table 21). Mean age at onset of migraine was 18.4 years in subjects with CAD and 19.2 years in controls. The corresponding figures concerning the typical length of attacks were 13.9 hours vs.17.9 hours, the number of moderate or severe attacks was 149.2 vs. 87.9 (P=0.19), the pulsating nature of headache was 50.0% vs. 50.0%, and the prevalence of the Raynaud phenomenon was 15.4% vs. 14.5%. Subjects with CAD reported more prodromal neck sensations associated to migraine (26.5%) than controls (9.3%) (P=0.02) as well as more vomiting, 71.1% vs. 50.0% (P=0.044).

Table 21. Migraine-related and vascular features in patients with cervical artery dissection and controls

	DISSECTION	CONTROLS	P VALUE
Age at onset (y)	18.4	19.2	0.64
Typical length of attack (h)	13.9	17.9	0.41
Number of moderate or severe attacks	149.2	87.9	0.19
Vomiting	71.1%	50.0%	0.044
Raynaud phenomenon	15.4%	14.5%	0.90
Prodromal neck sensation	26.5%	9.3%	0.021
Pulsating pain	50.0%	50.0%	1.0

Information about the influence of dissection on the activity of migraine was obtained from 57 CAD patients (figure 9), of whom 51% (29/57) reported decreased migraine activity immediately after CAD (complete remission in 13, significant decrease in 11, and slight decrease in 5). A minority of CAD patients reported a slight increase in migraine activity. The alleviation of migraine after CAD did not depend on whether the subjects suffered from stroke (50%; 18/36) or not (52%; 11/21). The rest (44%; 25/57) of the patients did not report any change in migraine activity after CAD, but in 48% (12 out of 25) of these patients, migraine was no longer active at the time of the dissection.

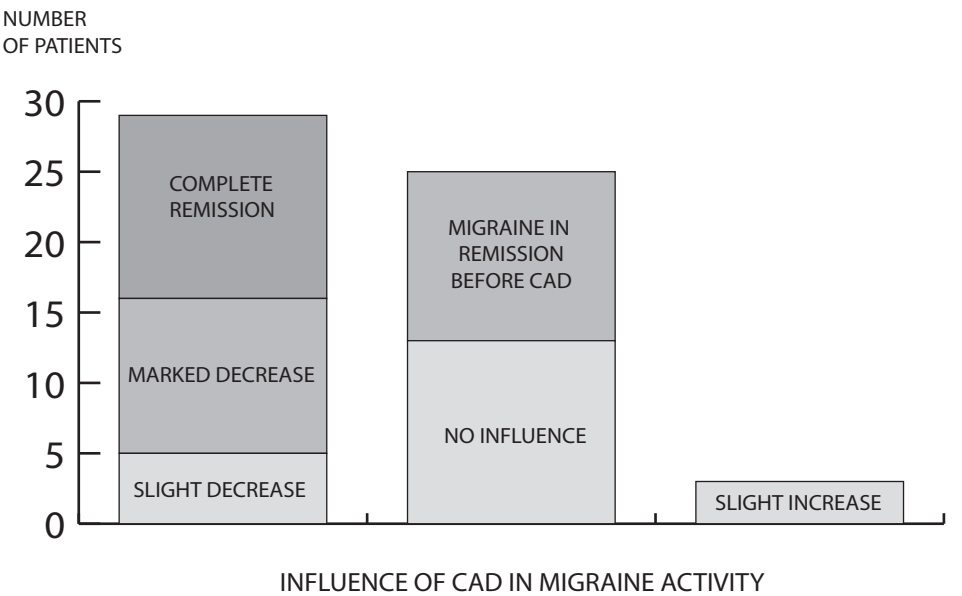


Figure 9. Distribution of the different reported effects of CAD in the activity of migraine.

10 Treatment of hemiplegic migraine with triptans (IV)

In the FMGP database, 198 patients had hemiplegic migraine fulfilling the ICHD-II criteria and the 76 (38.4%) of them had used triptans at least once as an abortive treatment of migraine were included in the study. The mean age was 42.9 and 92.1% (70 individuals) were female. FHM was diagnosed in 40 patients originating from 33 FHM families. 36 patients had SHM. The criteria of basilar type migraine were fulfilled by 37 patients (48.7 %). On average, the participants had used triptans on 257.2 occasions (SD +/-450.3). The average reported triptan response on a scale from 0 to10 was 6.9 (SD +/-3.1) and the distribution of reported responses are shown in table 22.

The average reported adverse event severity was 4.9 (SD +/-3.3) on a scale from 0 to 10. The distribution of reported adverse events are shown in table 23.

The most reported side effects were chest pain, nausea and fatigue. One patient reported unconsciousness and hemiparesis, and another patient reported hemiparesis. These symptoms had also occurred earlier during their attacks without triptan treatment. No one reported ischemic stroke or myocardial infarction as an adverse event. The distribution of reported side effects is shown in table 24.

Table 22. Distribution of reported responses to triptans in 76 patients with hemiplegic migraine selected from the Finnish Migraine Gene Project (FMGP)

TREATMENT RESPONSE	%
Excellent [a]	63.5
Moderate [b]	21.6
Poor [c]	14.9

[a] reported response from 8 to 10 on a scale from 0 to 10
[b] reported response from 3 to 7 on a scale from 0 to 10
[c] reported response from 0 to 2 on a scale from 0 to 10

Table 23. Severity of the reported adverse events to triptans in 76 patients with hemiplegic migraine selected from the Finnish Migraine Gene Project (FMGP)

TREATMENT ADVERSE EVENTS	%
Severe [a]	28.4
Moderate [b]	39.2
Mild [c]	32.4

[a] reported severity of adverse events from 8 to 10 on a scale from 0 to 10
[b] reported severity of adverse events from 3 to 7 on a scale from 0 to 10
[c] reported severity of adverse events from 0 to 2 on a scale from 0 to 10

Table 24. Distribution of the reported side-effects of triptans in hemiplegic migraine patients selected from the Finnish Migraine Gene Project (FMGP)

REPORTED SIDE-EFFECT	%
Chest pain	27.6
Nausea	26.3
Fatigue	22.4
Tachycardia	9.2
Confusion	6.6
Worsening of pain	5.3
Worsening of aura	5.3
Uncosciousness	2.6
Hemiparesis	2.6

One case of potentially permanent side effects was reported. A woman with migraine with aura belonging to a FHM family reported a severe migraine-like headache without aura symptoms, which she treated with 10 mg rizatriptan. She ended up in a central hospital due to walking difficulties, dizziness, ataxia, mild right side hemiparesis and visual disturbances. The hemiparesis persisted despite completely normal neuroradiological evaluations (brain MRI, brain MRI with cadolinium, MRA, cervical MRI and Doppler ultrasound of carotid vessels). After three months, azetazolamide treatment was started with the dramatic response of the reoccurrence of the symptoms. The patient continues to have occasional HM attacks. A follow-up MRI with 3T equipment was normal 6 years after the incident.

DISCUSSION

The data presented support the idea that migraine is a complex disease. Migraine has many faces, phenotypes, and sometimes it looks like each patient has migraine of her own. Therefore, the nature and genetic background of migraine has been difficult to resolve. One possible tool has been to evaluate the comorbidity of migraine. Many kinds of comorbidities have been suggested during past decades, but they have been either vague or have not led us nearer to origins of migraine. Results of this study highlight the complex neurovascular nature of migraine and contribute to the knowledge regarding neuronal, vascular, immunological and psychological aspects of migraine. Subjects suffering from migraine in the FMGP have an elevated risk for hypotension, allergy and psychiatric disorders and men who suffer from MA are more likely to have epilepsy and IS. Subjects with CAD have a higher prevalence of migraine than healthy controls and alleviation of migraine after CAD further indicates the association of these two conditions. Therefore, it seems likely that CAD is an important link between MA and IS. Overall, associations were especially evident with subjects with migraine aura or aura-like symptoms suggesting that the aura phase plays an important role in the comorbidity of migraine. Significant evidence of linkage was found between visual migraine aura and the chromosomal region 9q21–q22, a known occipitotemporal lobe epilepsy locus (241). It seems that triptans are safe and effective in the treatment of hemiplegic migraine.

Results of this study are consistent with numerous previous publications. In the studied population, allergy and psychiatric conditions were comorbid with migraine as previously reported (242-244). In a more detailed analysis, the disorders were especially prevalent with the phenotypes including aura (MA, MA+MO and UNC). Subjects belonging in category HA seem to have a trend comorbidities in similar fashion like migraineurs. This is understandable, as their headache might include some migraine features. However, not any of the comorbidities was significantly different from subjects without headache. The relationship between blood pressure and migraine has been controversial. Most of the studies that show association between hypertension and migraine have been done before the introduction of the ICHD. However, the most recent studies have associated migraine to hypotension (189, 190).

Prior studies have shown a clear association between migraine and epilepsy (196) and the link with epilepsy has been especially strong with MA (200). Several antiepileptic agents are effective in treatment of migraine (107, 110). Migraine and ep-

ilepsy are both episodic disorders associated with cortical hyperexcitability. In the present study, epilepsy was significantly associated with migraine among men only. Beyond clinical and epidemiological association, migraine and epilepsy partly share a common genetic background. All three known FHM genes (*CACNA1A*, *ATP1A2* and *SCN1A*) (8-10) have also been associated to epileptic seizures (41, 42). We found significant evidence of linkage between visual migraine aura and the chromosomal region 9q21–q22. This region stands out among other identified migraine loci because it had previously been linked to occipitotemporal lobe epilepsy in a Belgian family (241). The highest parametric linkage signal was detected when all subjects with aura were considered affected. The signal at this locus decreased when pure MA end-diagnosis or migraine headache were used as a selection criteria. The difference in Lod Scores suggests a direct link between this locus and the aura mechanisms.

Migraine and epilepsy can both be divided into several subgroups. These subgroups seem to differ in their pathophysiology and genetic background, but the shared mechanisms of migraine and epilepsy seem to exist only in certain of these subgroups. This means that a detailed analysis of the phenotypes, both in migraine and epilepsy, is the key for further studies. Careful analysis of the migraine aura, whether it includes hemiplegic, visual, sensory or speech symptoms, seems to be important (fig 10).

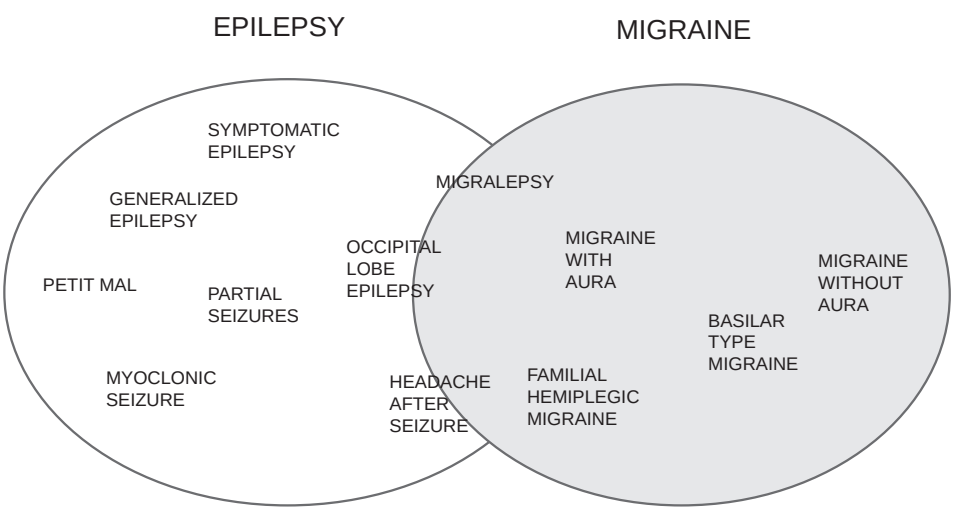


Figure 10. Association of epilepsy and migraine and their subgroups.

The association of migraine and stroke is well established (146, 147). However, in our consecutive families from the FMGP, the only significant finding was that men who fulfilled the criteria of both migraine with and without aura had an elevated risk for stroke. Association of migraine and stroke has been reported more convincingly in women than in men (132). Interestingly, the only previous exception to the rule so far has been another Finnish study (137). Therefore, it is possible that a shared genetic liability to these conditions is stronger in males in the Finnish population. Several clinical conditions have been suggested to contribute to the link between stroke and MA, but none of them alone are likely to explain the whole phenomenon (Fig. 11). Complicated migraine attacks rarely induce IS, an event called migrainous infarction (MI), which is probably a consequence of prolonged oligemia induced by CSD. However, CSD alone does not explain the association between migraine and ischemia, because even though its link to stroke is understandable, the connection with ischemic heart disease is more difficult to explain. Subjects with MA have been reported to have an increased prevalence of PFO (152), which is associated to IS (155). Subjects with migraine have been reported to have more traditional vascular risk-factors than subjects without migraine (193). However, migraine has not been associated to atherosclerosis in carotid vessels (245). An interesting connection between IS and migraine is CAD, which is known in the etiology of stroke and plays an especially important role in young stroke patients (164). CAD and migraine have been linked in a small series (166), but to the best of our knowledge, our report is the first study to show the connection between CAD and MA.

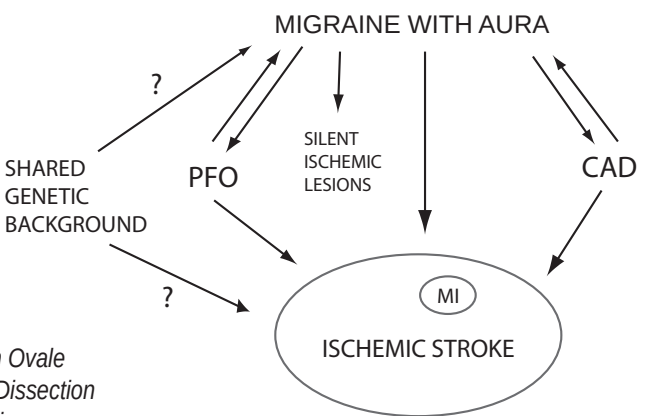


Figure 11. Illustration of associations between migraine with aura and ischemic stroke.

Increased knowledge of the comorbidity might be helpful in designing individual treatment strategies for subjects suffering from migraine. It seems that the comorbidity of migraine is especially evident and important among subjects with aura. Migraine seems to be associated to both neuronal (epilepsy) and vascular (IS, CAD) syndromes, thereby suggesting the importance of both of these phenomena in the pathophysiology of migraine.

There are several implications of the data when migraine pathophysiology and treatment are considered. Prophylaxis of stroke is important in familial migraine. Treatment of allergic conditions is important and could also cause migraine relief. Treatment of psychiatric conditions, especially depression, is an essential part of comprehensive migraine care. Antiepileptic medications could be especially good choices for migraine prophylaxis if there is a family history of comorbid epilepsy. From a pathophysiological point of view, studies involving ion channels (epilepsy), vascular systems (hypotension, IS and CAD), immunology (allergy) and serotonergic transmission (psychiatric conditions) are indicated. Besides therapeutical implications, this may be important when searching for the elusive genes causing the common forms of migraine. A locus for both migraine and epilepsy on chromosome 9q suggests a major target for further molecular genetic studies. Migraine families can be categorized based on their familial comorbidities and the resulting categories studied separately. This will, most probably, lead to more homogenous study populations, and increase the likelihood that current molecular genetic methods will locate new migraine genes increases.

Migraine pathophysiology involves dysfunction in both neuronal and vascular systems, but in recent years the focus has generally been on the neuronal system. Our results associating migraine to an arterial disorder suggest that vascular system phenomena should not be overlooked. There is reasonable evidence indicating that both migraine and CAD are multifactorial diseases with genetic predisposition (246). As PFO and CAD are linked to migraine, all the conditions might represent inherited disturbance of vascular endothelin function and explain the comorbidity. CAD patients may have a constitutional, genetically determined weakness of the vessel wall, and environmental factors, such as acute infection or minor trauma, could act as triggers. It remains to be elucidated whether a mutual arterial pathophysiology shared by CAD and migraine, or simply a concomitant inherited suspectibility, exists. The reported alleviation of migraine after CAD supports the hypothesis of some causal relationship between these diseases. It seems, that alleviation of migraine was linked to CAD independently from IS. The role of CAD and IS treatments, such as

anticoagulants and antihypertensive medications, remain unclear.

Subjects with HM have been excluded from all prior triptan studies (53). Our study demonstrates that triptans are effective for most of the HM patients. Several adverse events were reported, but almost all of them were transient and were either the result of typical triptan side effects (thoracic pain, nausea and fatigue) or the symptoms of normal migraine attacks. One patient reported alarming long lasting symptoms: mild hemiparesis, ataxia, walking difficulties, dizziness and visual disturbances for several months. However, a stroke seems unlikely, because none of the several MRI studies demonstarted ischemic signs or any other pathology. Most likely, the patient had an unusually long lasting attack of HM. Therefore, the role of rizatriptan remains unclear, but it is possible that it either induced or enhanced these symptoms. Triptans seem to be safe in the treatment of FHM, but they should be used with caution. Triptans work for both FHM and migraine without aura suggesting that the disorders are part of a common spectrum.

Some reservations are appropriate when analyzing the presented data. The applied questionnaire, the FMSQFS (236), has been validated for migraine but not for the associated diseases. The studied populations are clinical or family-based, they are not population-based samples. Therefore, as results of the study can not be generalized straightforwardly and precise incidence or prevalence figures cannot be drawn from the data, the focus has to be placed on the reported differences between the studied groups. Analysis of migraine aura with the questionnaire can be criticized as a too robust method for such a delicate phenomenon. However, possible problems should be similar in all studied groups. The nature of the possible aura was assessed in several different ways by the FMSQFS and in many cases clinical features were re-evaluated in a telephone interview. Self-reporting of coexisting conditions is also problematic. Especially in conditions such as psychiatric disorders, laboratory parameters and blood pressure. We are aware of the short comings of these results with respect to its validity. When analyzing blood pressure of a individual from a questionnaire, it is impossible to know whether the reported result is based in perhaps only one, and therefore unreliable measurement. On the other hand self-reporting should be relatively reliable in conditions such as epilepsy, allergy, asthma, stroke.

One of the limitations of the family-based linkage method is that the linked region is typically large, harboring dozens of genes. A case-control association study targeted to the linked 9q21-q22 region might provide a better resolution. However, a large sample size with similar phenotype, i.e. scintillating scotoma, is not currently available, but might be possible to achieve

with international collaboration. Additionally, a proportion of men was too small for a reliable sex-specific linkage analysis.

The prevalence of migraine has been generally estimated to be 10 to 12%, but higher numbers of lifetime prevalence have also been reported (23, 247). In study III, the prevalence of migraine was exceptionally high, up to 22% in control group. No population-based studies of migraine prevalence in Finland exist, but prevalence is likely comparable to that in other Northern European countries (248). Controls were recruited randomly with the help of the Finnish Population Register Center and interviewed by a study-neurologist as a part of a larger study, not focused on migraine. Therefore, possibility of a bias should have been minimized. Importantly, patients suffering from CAD still had significantly more migraine regardless of the high prevalence numbers in the controls.

The chosen retrospective setting in study IV is not optimal, but it would not be possible or even ethical to carry out a prospective study with a compound that is contraindicated in the study population. It can also be argued that it would be optimal if the diagnosis of HM were based on molecular genetic data. While this would naturally add value to our study, in most instances this would be very difficult and our neurologist-based diagnoses reflect the real-life clinical situation and are in accordance with the current ICHD-II criteria (2).

A novel techniques, such as GWA, will hopefully shed light to genetics and basic mechanisms of migraine. Our recent GWAs in MA patients identified a sequence variant on chromosome 8q with significant association to migraine with aura (Anttila *et al.*, submitted). The expression quantitative trait study in lymphoblastoid cell lines showed a strong correlation between the variant and transcript level of a nearby downstream gene, that has long been suspected to play a key role in migraine pathophysiology through glutamate-mediated neuronal hyperexcitability (249). The results of the meta-analysis strongly suggest the existence of a shared underlying mechanism for the two main forms of migraine (MA and MO). However, it will be important in the future studies that migraine is phenotyped as accurately as possible. This has turned out successful in genetic studies of migraine (50) and similar efforts are needed in clinical and therapeutic studies. It will be important to figure out individually what kind of medications are best for certain patient and to know better which patients are in major risk for serious complications, such as ischemic stroke or chronification of migraine.

CONCLUDING REMARKS

Careful analysis of migraine comorbidity is one of the possible clinical strategies to subgroup migraine population for further analysis. Vascular, immunological and psychiatric aspects are all important. Epilepsy and stroke are very important comorbidities, but their prevalence in the migraine population depends heavily on the target population (migraine families, aura families, population-based studies). Sometimes a vascular pathology can be a provoking factor for migraine, or at least it may cause an increase in migraine frequency. Triptans work in the headache phase of all subgroups of migraine (MO, MA and FHM), suggesting that the various migraine subgroups have similar pathophysiological mechanisms during the headache phase. The aura seems to differ more between various subgroups of migraine, perhaps creating an important tool for better phenotyping of migraine patients. This has consequences on genetic, epidemiological and even clinical studies of migraine. Migraine phenotypes and migraine comorbidity are complex. However, it seems that these complexities have to be taken into consideration before the pathophysiology of migraine can be made simple.

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Ville Artto

Helsinki, April 2010

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